Acta Pædiatrica

Vol. 40 · April 1951 · Suppl. 80

UNIVERSITY OF MICHIGAN
JUL 27 1951
MEDICAL LIBRARY

ERIK FRISELL

STUDIES ON BACTERIUM BIFIDUM IN HEALTHY INFANTS

A Clinical Bacteriological Investigation

Almqvist & Wiksells Boktryckeri AB UPPSALA

UNIVERSITY OF MICHIGAN LIBRARIES

List of Supplements to Acta Pædiatrica.

Vols. 1—40 (1923—1951).

1. **Muhl, Greta,** Über den Stoffwechsel des gesunden, natürlich ernährten Säuling- und dessen Beeinflussung durch Fettreduktion der Nahrung. Sw. Cr. 5: —.
2. **Höjer, J. Axel,** Studies in Scurvy. Sw. Cr. 5: —.
3. **Eriksson, Zaida,** Über Anstaltsschaden der Kinder: »Hospitalismus» in Kinder heimen. Sw. Cr. 3: —.
4. **Drucker, Paul,** Clinical Investigations into the Pathogenesis of Infantile Tetany Sw. Cr. 3: —.
5. **Wallgren, Arvid,** Contribution à l'étude des splénomégalies de l'enfance. Sw. Cr 5: —.
6. **Rhodin, Hans,** The Suspension-Stability of the Blood in Scarlatina. Sw. Cr. 3: —
7. The Proceedings of the Fourth Scandinavian Pædiatric Congress, held at Helsingfors on June 28th—30th, 1927. Sw. Cr. 5: —.
8. **Herlitz, C. W.,** Studien über die Blutzuckerregulierung bei gesunden Säuglingen und solchen mit exsudativer Diathese. Sw. Cr. 3: —.
9. **Widnäs, Karin,** Études sur le diabète sucré chez l'enfant. Sw. Cr. 5: —.
10. **Gyllenswärd, Curt,** Some Sources of Error at Differential Count of White Corpuscles in Blood Stained Smears. Sw. Cr. 3: —.
11. **Salomonsen, Leif,** Periodisches Erbrechen und Ketonämie bei Kindern. Sw. Cr 5: —.
12. **Wallgren, Arvid,** Erfahrungen über epidemischen Icterus (sog. Icterus catarrhalis). Sw. Cr. 5: —.
13. **Rietz, Einar,** Sterblichkeit und Todesursachen in den Kinderjahren. Sw. Cr 5: —.
14. **Gyllenswärd, Curt,** Das weisse Blutbild bei Hunger und regelmässiger Nahrungszufuhr. Sw. Cr. 3: —.
15. **Skaar, T.,** Experimental Rickets. Sw. Cr. 5: —.
16. **Toverud, Kirsten Utheim,** and **Toverud, Guttorm,** Studies on the Mineral Metabolism during Pregnancy and Lactation and its Bearing on the Disposition to Rickets and Dental Caries. Sw. Cr. 5: —.
17. **Kloster, Johan,** The Distribution and Frequency of Rickets in one of the Fisher Districts of Finmark and Relation of Diet to the Disorder. Sw. Cr. 5: —.
18. **Svensgaard, Elisabeth,** Blood Sugar in Normal and Sick Children with Special Reference to Coeliac Disease. Sw. Cr. 5: —.
19. **Herlitz, C. W.,** A Contribution to the Knowledge of the Function of the Liver and the Reticulo-Endothelial System, Particularly in Infectious Diseases of Children. Sw. Cr. 3: —.
20. **Henschen, Folke,** Über Christians Syndrom und dessen Beziehungen zur allgemeinen Xanthomatose. Sw. Cr. 3: —.
21. **Bjørn-Hansen, Haakon,** Leukozyten-Untersuchungen bei den Masern. Sw. Cr 5: —.
22. **Joukovsky, V. P.,** et **Rousskikh, V. N.,** Étude clinique et anatome-pathologique sur la tuberculose des centres nerveux chez l'enfant. Sw. Cr. 3: —.
23. **Huss, Ragnar,** Studien über die Schultz-Charltonsche Auslöschreaktion bei Scharlach. Sw. Cr. 5: —.
24. **Wickström, J.,** Eine elektrokardiographische Untersuchung über das Herz bei Scharlach. Sw. Cr. 3: —.
25. **Schiøtz, Carl,** Eine Darstellung und kritische Bewertung der Ursachen des Rückganges der Säuglingssterblichkeit in Norwegen. Sw. Cr. 5: —.
26. The Proceedings of the Sixth Northern Pediatric Congress, Stockholm August 27—August 29, 1934. Sw. Cr. 5: —.
27. **Rustung, Erling,** Studien über Rachitis. I. Mitteilung. Sw. Cr. 3: —.
28. **Sundal, Alfred,** Chronische infektiöse Erkrankungen der Harnwege im Kindesalter. Sw. Cr. 3: —.
29. **Magnusson, J. Henning,** Zur Kenntnis der Blutveränderungen bei Frühgeborenen. Sw. Cr. 5: —.
30. **Herlitz, C. W.,** Studien über den Krankheitsverlauf und die Therapie des Diabetes mellitus bei Kindern. **Söderling, B.,** Behandlung der Zuckerkrankheit im Kindesalter ohne Diäteinschränkungen. Sw. Cr. 5: —.
31. **Ström, Justus.** Periodisches Erbrechen mit Ketonämie bei Kindern. Sw. Cr. 5:
32. **Faxén, Nils,** The Red Blood Picture in Healthy Infants. Sw. Cr. 5: —.

Errata

Page 5, line 10: for *Damm*, read *Dam*.
Page 14, line 15 should read: *Ascorbic acid (or cysteine 2 g) ... 1 g.*
Page 14, line 16 should read: *Sodium azide (NaN_3) 10 per cent ... 1 ml.*
Page 16, Fig. 1: for *1: 10^{-2}, 1: 10^{-5}, 1: 10^{-6}, 1: 10^{-7}, 1: 10^{-8} and 1: 10^{-9}*, read *1: 10^{2}, 1: 10^{5}, 1: 10^{6}, 1: 10^{7}, 1: 10^{8}, and 1: 10^{9}*.
Page 16, last line: for *1: 10^{-6}*, read *1: 10^{6}*.
Page 17, line 1: for *1: 10^{-9}*, read *1: 10^{9}*.
Page 25, Fig. 2: for (*see Table 3*). *The broken line ...* read (*see Table 3*). *Logarithmic scale. The broken line ...*
Page 27, Table 4 should be continued as below:

(Table 4 cont.)

Date	Faeces		Millions of Bacteria per 1 g of Faeces		
	Odour	pH	Coliform	Growing on Dextrose Agar	Bact. Bifidum
G. Q. Born 28.8.50					
21.9	A	6.0	130	235	1 800
29.9	»	5.8	39	<100	1 100
4.10	»	5.2	<1	32	6 500
16.10	»	5.6	<1	11	29 000
28.10	»	5.5	56	640	34 000
E. O. Born 22.4.50					
8.5	A	6.6	4	1 030	88 000
22.5	»	5.0	780	1 700	9 900[1]
1.6	F	6.7	1 440	2 520	110
12.6	»	6.1	352	670	13 000
26.6	»	7.4	830	2 630	108 000
J. K. Born 2.7.49					
14.9	A	5.3	520	630	5 800
21.9	»	5.2	40	120	19 800
24.9	»	4.4	180	550	29 000
1.10	»	4.4	130	250	46 000
14.10	»	5.4	760	760	3 400
21.10	(A)	6.4	305	322	21 000

[1] Somewhat too low due to fault in culture medium.

UNIVERSITY OF MICHIGAN LIBRARIES

Page 40, line 1: for (*S. H. and H. Z.*) read (*S. H. and Å. Z.*).
Page 40, line 6: for *G. Z.* read *Å. Z.*
Page 50, Fig. 10: for *C. L.* read *C. D.*
Page 67, last line: for *A. O. and K. E.*, read *A. O. and K. L.*
Page 83, line 8 from below: for *M. O., M. S., and M. H.*, read *M. O., Å. S., and M. H.*
Page 83, line 7 from below: for *Å. S. and S. H.* read *Å. Z. and S. H.*
Page 90, Table 25: for *Value* % read *Values* %.
Page 104, line 13: for *6.3* read *6.2.*
Page 106, line 2: for *13.000* read *13 000.*
Page 106, line 3: for *8.400* read *8 400.*

FR

PE

FROM THE SACHS HOSPITAL FOR CHILDREN, STOCKHOLM, SWEDEN
PHYSICIAN-IN-CHIEF: DOCENT J. HENNING MAGNUSSON, M. D.

STUDIES ON BACTERIUM BIFIDUM IN HEALTHY INFANTS

A Clinical Bacteriological Investigation

By ERIK FRISELL

UNIVERSITY OF MICHIGAN LIBRARIES

Acta Pædiatrica, Supplementum 80

UPPSALA 1951
ALMQVIST & WIKSELLS BOKTRYCKERI AB
516603

Contents

Page

Preface 5
Historical Introduction 7
Personal Investigations
Purpose of Investigation 10
Terminology 10
Bacteriology 12
Method 13
Error of Method 17
Discussion of Method 19

Chapter I. Breast Feeding
Earlier Investigations 21
Case Material 21
Results 22
Summary 28

Chapter II. Feeding on Heated Breast Milk
Earlier Investigations 29
Case Material 29
Early Results 30
Late Results 38
Clinical Observations 42
Summary 43

Chapter III. Bottle Feeding
Earlier Investigations 45
Case Material 45
Results 46
Summary 53

Chapter IV. Supplemented Breast Feeding
Earlier Investigations 54
Personal Investigations 54
Results 55
Summary 58

Chapter V. Feeding on Mixed Diets
Earlier Investigations 59
Personal Investigations 59
Summary 61

UNIVERSITY OF MICHIGAN LIBRARIES

Chapter VI. Oral Administration of Alpha and Beta Lactose Page

Introduction and Earlier Investigations 62
Personal Investigations 65
Case Material 66
Results 67
Discussion 72
Summary 74

Chapter VII. Tests of the Susceptibility of Bacterium Bifidum to Antibiotics and Sulphonamide

Earlier Investigations 75
Personal Investigations 75
Case Material 75
Method 76
Tests in Vivo 76
Tests in Vitro 76
Results 77
Clinical Observations 85
Summary and Discussion 86

Tabulation of Results Described in Chapters I, II, III, and V 89
General Summary and Discussion 89
Conclusions 95
Bibliography 120
Plates.

Preface

The impulse for the present investigation into the occurrence of *Bacterium bifidum* came from Docent J. Henning Magnusson, my then teacher and chief. It is a pleasant duty to record here my deep gratitude to him for his advice and encouragement and for following the work with such keen interest.

I owe a great debt of gratitude to the late Dr. Erik Olsen, of Copenhagen, who taught me the bacteriological technique and who was so accommodating and helpful during my visits to the Danish capital.

My thanks are also due to Professor H. Damm, of the Danish Institute of Technology, Copenhagen, who very kindly arranged working facilities for me at his institution and provided material for culture media.

For his kindness in going through the manuscript I am indebted to Professor Sven Gard.

I wish to thank Docent Greta Hammarsten and Dr. Gunnar Laurell for valued advice and suggestions during the course of the investigation.

Miss Maud Persson acted as my assistant throughout the work and, among other things, did all the bacteriological cultures. I greatly appreciate her unselfish and painstaking work and her invaluable help in general.

My grateful acknowledgements are due to the nursing staff of the Sachs Hospital for Children, in particular Sisters Greta Granberg, Anna-Lisa Håkansson, Gerd Struve, and Dagny Jonsson, for valuable assistance with the clinical tests.

Mr. Gunnar Blom, Ph. L., of the Statistical Research Group of the University of Stockholm, did the statistical calculations. I wish to thank him both for his excellent work and for useful advice.

Lastly, I am indebted to Mr. Stanley H. Vernon for his interest and for his careful translation of this paper into English.

Umeå, March, 1951.

Erik Frisell

UNIVERSITY OF MICHIGAN LIBRARIES

Historical Introduction

The relationship between food and the intestinal flora has always been a burning problem in medicine. TISSIER's discovery of *Bacterium bifidum* (1900), and his study of its occurrence in the stools of infants, afforded facts of lasting value from the paediatric standpoint. It was in particular the finding that the breast-fed infant occupies a unique position with respect to bifidum flora which played a major role in the subsequent discussion. For Tissier found that in such infants *Bact. bifidum* comprised practically the entire intestinal flora, whereas in artificially fed infants it occurred to an appreciably lesser extent together with a number of other bacteria.

Perhaps due to imperfect bacteriological technique, a number of investigators have failed to verify the occurrence of *Bact. bifidum* in artificially fed infants. Bifidum flora has, therefore, been interpreted as a qualitative characteristic of breast-fed infants. Actually it is the quantity of bifidum which is specific, particularly in relation to the inconsiderable number of other bacteria. For paediatricians, bifidum flora stood out as "a valuable indicator of the normal course of the digestive processes" (BESSAU, 1937), and it was therefore aimed at in the feeding of all infants. If it were possible with artificial feeding to provoke bifidum flora in the stools, this was considered to prove that the mixture used had properties which essentially were comparable with those of breast milk.

The view put forward by TISSIER has, however, been confirmed in principle by the studies of BLAUROCK (1937), OLSEN (1949) and the present writer, amongst others. In order to solve the problem quantitative methods must, therefore, be used.

In the course of the years, intensive research and speculation have been devoted to the problem of the nature of the factor in breast milk which gives rise to this particular bifidum flora.

UNIVERSITY OF MICHIGAN LIBRARIES

Various authors have considered themselves able to demonstrate that the cause is to be sought in certain peculiarities in the content of fat, lactose, amino acid complexes, etc., in breast milk. MORO (1907) claimed to have established by the feeding of infants and young dogs with boiled breast milk, that there is a thermostable factor in this milk which determines the bifidum flora; in his opinion the sugar and the fat are of no major importance. BESSAU came to the conclusion that it is the whole chemical composition of breast milk which is the decisive factor, and not the individual details of it. OLSEN (1949) also held this view in principle.

BESSAU showed too (1943) that the growth of bifidum may be totally or partially inhibited e.g. by the administration of Spirozid, without any clinically demonstrable symptoms of intestinal disorder. As a result of this finding, BESSAU abandoned his earlier view (see above) and instead considers that "the observations may indicate that the bifidum flora does not constitute a *sine qua non* for optimal digestion".

PETUELY and KRISTEN recently stated in a preliminary report (1949) that they had discovered and isolated a bifidum-stimulating substance. If a daily quantity of 10 mg of this substance was added to the food of an artificially fed infant, a practically pure bifidum flora, such as is only found in the stools of breast-fed infants, was obtained after 24 to 36 hours. At the same time the stools assumed the characteristics of those of breast-fed infants, and had a pH between 5.0 and 5.6. The tests could be duplicated in dogs. The changes in the faecal flora were apparently studied only by microscopic examination of stained smears. In a subsequent report PETUELY and KRISTEN (1950) state, however, that the substance does not have any direct action on the growth of bifidum, but inhibits *in vitro* the other intestinal bacteria.

The occurrence of *Bact. bifidum* in healthy persons under various nutritional conditions has only been very imperfectly investigated hitherto. ORLA-JENSEN, OLSEN, and GEILL (1945), using a quantitative method devised by OLSEN, studied its occurrence in adults and senile persons. They found that the bifidum count in adults in their series ranged between 100 million and

10 000 million per gramme faeces, that it fell markedly in senility with decreasing gastric acidity, and that the diet in these cases did not play any conspicuous role. OLSEN (1949) also investigated with the same method the number of bifidum bacteria in a series of infants from birth onward during different phases of feeding. (See pages 21 and 45.) However, the series did not permit any definite conclusions concerning the relation between breast-fed infants and infants not fed on breast milk.

The large number of other investigations into the bifidum flora in infants have resulted in vague conclusions, which are difficult to appraise since no quantitative methods were employed.

The question of when and in what manner the newborn infant becomes infected with *Bact. bifidum* has been the subject of several investigations. This was particularly the case at a stage when the occurrence of *Bact. bifidum* in the adult intestine had not been verified. Transmission of the bacterium from the mother's intestine to the infant's alimentary canal at parturition is suggested by the investigations of e.g. MAASSEN and ALBERTSEN (1940) and ROUFOGALIS (1941). No proof of transmission via the breast milk has earlier been advanced. MOSER (1950), however, recently succeeded in culturing *Bact. bifidum* under certain conditions from cow's milk and human milk and from fresh udder tissue from cows.

In the newborn infant, *Bact. bifidum* commences to appear in the faeces between the second and fifth day of life (TISSIER, 1900; WEISS and RETTGER[2], 1934; MAASEN and ALBERTSEN, 1940; OLSEN, 1949), though it is never the first species of bacterium to occur there. OLSEN was able to demonstrate both micrococci and enterococci, and coliform and clostridia prior to the appearance of bifidum.

UNIVERSITY OF MICHIGAN LIBRARIES

Personal Investigations

Purpose of Investigation

The primary aim of the present investigation was, with the use of the quantitative method of OLSEN, to elucidate the occurrence of *Bact. bifidum* in healthy infants and under the following conditions:

I. Breast feeding.
II. Feeding on heated breast milk;
  (a) full-term infants;
  (b) premature infants.
III. Bottle feeding.
IV. Supplemented breast feeding.
V. Feeding on mixed diets (including children over 1 year).
VI. Oral administration of alpha and beta lactose.
VII. Tests of the susceptibility of *Bact. bifidum* to antibiotics and sulphonamide.

Terminology

By "breast-fed infants" is meant infants of 0 to 5 months who were fed solely at the mother's breast from birth.

By "heated breast milk" is meant expressed breast milk which was either heated to 100° C or pasteurised at 68° C for 10 minutes.

By "bottle-fed infants" is meant infants between the ages of 0 and 6 months who were fed solely on cow's milk formula for at least two weeks prior to the examination. The duration of feeding solely on the bottle is given alongside the age.

The cow's milk formula used in the present investigation consisted either of citric acid milk containing 7 per cent sugar but no flour, or of half-milk formula containing 5 per cent sugar and 3 per cent flour.

By "mixed diets" is meant diets containing no breast milk and composed of solid foods, soups, gruel, porridge, fruit, etc.

The term "other bacteria" denotes, except where otherwise stated, bacteria found on culturing on endoagar (coliform) and on 2 per cent dextrose agar. Since these two groups were of the same order of magnitude throughout the investigation, the number of the latter has represented "other bacteria" in certain comparisons with the bifidum count.

The following statistical terms and formulae will be used in this thesis:

By "mean value" is meant, unless otherwise stated, the geometrical mean of the observed values ($10^{\bar{x}}$).

The logarithm of the observed number of bacteria, etc. per unit faeces is presumed to be normally distributed, with mean m and standard deviation σ. Therefore, logarithmic values have been used in all calculations.

$\bar{x} = \dfrac{x_1 + x_2 \cdots + x_n}{n}$ = mean of logarithmic values (estimate of m)

$s = \sqrt{\dfrac{\sum (x - \bar{x})^2}{n-1}}$ = standard error of x (estimate of σ)

$\dfrac{s}{\sqrt{n}}$ = standard error of $\bar{x}$

$\sqrt{\dfrac{s_1^2}{n_1} + \dfrac{s_2^2}{n_2}}$ = standard error of the difference between two mean values with standard errors $\dfrac{s_1}{\sqrt{n_1}}$ and $\dfrac{s_2}{\sqrt{n_2}}$ respectively.

The significance of the difference has been tested by computing $t = \dfrac{\text{difference}}{\text{standard error}}$. If no difference exists between the means of the two populations compared, t is approximately t-distributed with $f = n_1 + n_2 - 2$ degrees of freedom (WELCH, 1938). When $f > 30$, the percentage points differ only slightly from the normal deviates given below.

The significance of a product moment coefficient of correlation r has been tested by $t = \sqrt{n-2} \cdot \dfrac{r}{\sqrt{1-r^2}}$. If the true

UNIVERSITY OF MICHIGAN LIBRARIES

coefficient of correlation is zero, t is t-distributed with $n-2$ degrees of freedom.

The following significance levels will be used in this thesis:

	Normal deviate	Probability level
Not significant	<1.96	<95 %
Significant*	1.96—2.58	95 %—99 %
Significant**	2.58—3.29	99 %—99.9 %
Significant***	>3.29	>99.9 %

Bacteriology

Bact. bifidum is an obligate anaerobic gram-positive, rod-shaped bacterium. Using tomato agar in tall columns, the colonies are as a rule quite large—2 to 3 mm in diameter—and generally china-white. Occasionally they have a reddish tint, apparently due to colour absorption from the added tomato. The colonies are lens shaped, quite often with the formation of a secondary lens at a right angle to the first. They are rarely closer than about 1 cm to the surface. The colonies, when touched with the inoculation needle, are often found to be so firmly connected that the whole colony is removed. When rubbed out in a drop of water, such a colony approximates to a coarse powder. Even under strictly anaerobic conditions, *Bact. bifidum* may grow in the form of surface colonies (on e.g. Blaurock's medium). A differentiation has been made between an 'S' type and an 'R' type (BLAUROCK, 1937, BOVENTER, 1938, and others), the latter being rare in infants (OLSEN, 1949, and others). Further, MALYOTH and BAUER (1950) have described an 'M' (mucoid) type. Microscopically, scarcely any difference can be noted between the cells in the three types of colonies.

There are fairly considerable variations in the microscopic picture. The following three main types are found, between which all transitions may be noted: small, almost regular rods, (Figs. 39 and 40), branched cells (Fig. 41) and club-shaped cells (Fig. 42). The last-mentioned may vary from short, thick, almost spherical bacteria, to long slightly curved, or 'S' shaped; somewhat thicker at one or both ends. Of these, one or more with

single or double branchings are found in almost every visual field. When the colonies contain small rods, the microscopic examination is facilitated by the fact that single, larger and thicker bacteria with a characteristic appearance are always present (Fig. 43). At times, particularly in older colonies, the stroma is gram-negative with gram-positive, round or staff-shaped globules. These are often located in the ends or at the bifurcation (Fig. 44). Just as little as the various forms of colonies, do these varying microscopic pictures correspond to morphologically distinct types of bacteria; rather they are conditioned by factors chiefly of exogenous nature (MAYER and MOSER, 1949).

Bact. bifidum is an obligate intestinal bacterium and is pronouncedly acid-forming. According to OLSEN (1949), the optimal pH is 6.5 to 7, and the upper and lower limits 4 and 9. The optimal temperature is 38° to 39° C, with 20° and 46° C as the limits. The critical temperature is 55° C. The presence of *Bact. bifidum* has been demonstrated in the faeces of, for example, the calf, the dog and the rat, in addition to man.

Bact. bifidum has earlier been classed, e.g. by ORLA-JENSEN (1943), as a lactic acid bacterium. In Bergey's "Manual of Determinative Bacteriology" (1950) it is also assigned to that category. Several other investigators are inclined, however, to regard it as a Corynebacterium. OLSEN (1949) has suggested the name *Corynebacterium bifidum*.

Method

The method employed in the present quantitative investigation of *Bact. bifidum* was devised by OLSEN (1945).* The culture medium on which it is based consists of a tomato agar originally described by WEISS and RETTGER[1] (1934), and subsequently modified by ORLA-JENSEN (1943). The cultures are made in Burri tubes. Two minor modifications were made in the original procedure: first, 0.01 per cent sodium azide (NaN_3)

* The principles of the method were mainly learnt under the instruction of E. OLSEN, Orla-Jensen's successor as Director of the Bacteriological Department of the Danish Institute of Technology, Copenhagen. A number of the ingredients of the culture media, *i.e.* casein peptone and yeast autolysate solutions, were supplied by that laboratory.

UNIVERSITY OF MICHIGAN LIBRARIES

was added to the medium to prevent the growth of coliform bacteria (LICHSTEIN, 1941), and, secondly, the faecal samples were diluted with a slightly different method (see Fig. 1).

The bacteriological section of the investigations proceeded for 3 $^1/_2$ years, with the help of one and the same laboratory assistant, at the Department of Bacteriology, Södersjukhuset, Stockholm.

Culture Media

Tomato Agar for Bifidum Culture (According to Orla-Jensen)

Casein peptone solution (N = 1 per cent)	100 ml
Yeast autolysate solution (N = 1 per cent)	100 ml
Peptone (Difco-Bacto Lab.)	5 g
Tomato purée (Bäncke)	50—60 g
Tap water	800 g
Dextrose 2 per cent	20 g
Ascorbic acid ~~0.1 per cent~~ (or cysteine, ~~0.2 per cent~~)	1 g
Sodium azide (NaN_3), ~~0.010~~ per cent	~~0.1~~ g

Casein peptone.—Casein powder 80 g, pepsin (1:900) 2 g, tap water 700 g, concentrated hydrochloric acid 10 g, are mixed in a glass flask, which is then closed with a cotton-wool plug soaked in chloroform. The flask is kept in a thermostat at 38° C for 12 days, being shaken each day; after which the contents are removed and filtered. Sodium phosphate 4 g per litre, and magnesium sulphate 2 g per litre are added to the filtrate. The pH is adjusted to 6.7. The mixture is then transferred to smaller flasks and autoclaved at 115° C for 15 minutes.

Yeast autolysate.—Three litres distilled water is boiled and then cooled to 60° C. Four kilogrammes dry yeast is crushed in the water to form a homogeneous mixture. This latter is then poured into a sterile container fitted with lid, and heated to 49—50° C in a water bath, thereafter being kept in a thermostat at that temperature for 4 days. (The container must be sufficiently large and have a well fitting lid.) The solution formed is then heated to 105° C for 30 minutes, and thereafter filtered. The filter paper and contents are mixed with 0.5 litres water in a dish, then heated to 60° C and filtered. Both filtrates are mixed, and now contain approximately 1 per cent nitrogen. The pH is adjusted to 6.0—6.7 and the mixture autoclaved at 115° C for 15 minutes.

The peptone is dissolved in part of the water and mixed, by careful stirring, with the yeast autolysate, casein solution and tomato purée. The mixture is then brought to the boil. Approximately 15 g (preferably chopped) agar is melted in the remainder of the water and added to the mixture.

The mixture is chilled to approximately 40° C, and the white of one egg, suspended in approximately 50 ml of water, then added. A check is made that the pH is below 7, as some of the amino acids and part of the vitamin B content of the culture medium are destroyed on heating in an alkaline environment.

The mixture is autoclaved at 115° C for 10 minutes, and then filtered until the medium is as clear as possible. The quantity obtained is measured. The pH is adjusted to 6.9. The glucose, ascorbic acid and sodium azide are added. The ascorbic acid is dissolved in a little water and adjusted to a pH of approximately 6. (Cysteine hydrochloride can be substituted for part of the ascorbic acid.) The solution is poured into tubes with 10 ml in each. It is sterilised once at 120° C for 8 minutes and then quickly cooled. The final pH should be 6.4 to 6.5.

In the present investigation, sodium azide was added to the original prescription, in order to prevent the growth of *Bacterium coli*, which at times ferments the column of culture medium and makes the reading difficult or impossible. Tests made by the writer have shown that sodium azide in this concentration does not demonstrably affect the growth of *Bact. bifidum*.

The tubes used were of splinter-proof glass, with both ends open. One was closed with a rubber stopper and the other with a plug of cotton wool (Burri tubes).

In addition, endoagar and 2 per cent dextrose agar were used in the cultures.

Endoagar

1. Meat extract (Difco-Bacto) 3 g; 2. Peptone 10 g; 3. NaCl 3 g; 4. Na_2HPO_4 12 H_2O 2 g; 5. Agar—agar 15—20 g; Tap water 1000 ml.

Ingredients 1 to 4 are dissolved by boiling in 500 ml of water. No. 5 is stirred in 500 ml of cold water and all the ingredients are then mixed in a vessel of glass, enamel or stainless steel, alkalised to pH 8.2 and boiled in the autoclave for 30 minutes at 120° C, filtered through a cotton filter and the pH adjusted to 7.4.

Ten grammes of lactose and 5 ml of saturated alcoholic fuchsin solution are added to 1000 ml of filtered agar and sterilised in streaming steam for 30 minutes for three consecutive days. On use, the endoagar is decoloured with approximately 10 ml of 10 per cent freshly prepared sterile sodium sulphite solution.

Dextrose Agar

The agar is prepared in the same way as for the endoagar. After filtration the pH is adjusted to 7.6. The agar is added as well as 2 per

UNIVERSITY OF MICHIGAN LIBRARIES

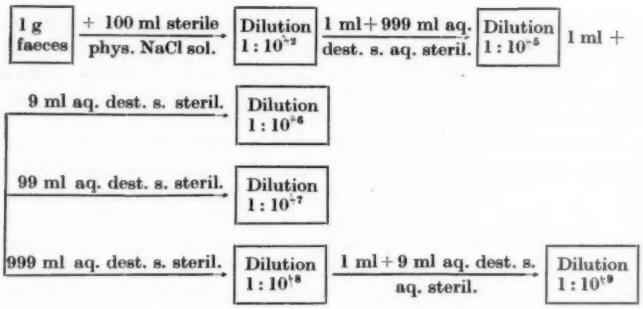

1 g faeces
+ 100 ml sterile phys. NaCl sol.
Dilution 1 : 10^-2
1 ml + 999 ml aq. dest. s. aq. steril.
Dilution 1 : 10^-5
1 ml +
9 ml aq. dest. s. steril.
Dilution 1 : 10^-6
99 ml aq. dest. s. steril.
Dilution 1 : 10^-7
999 ml aq. dest. s. steril.
Dilution 1 : 10^-8
1 ml + 9 ml aq. dest. s. aq. steril.
Dilution 1 : 10^-9

Fig. 1. Procedure used in diluting the faeces.

cent dextrose, sterilised in streaming steam for 30 minutes during the course of three consecutive days, or for 30 minutes at 120° C once only. After sterilisation the pH should be 7.2.

The samples of the faeces were taken from the infants' diapers or directly from the ampulla recti, and transferred to a carton fitted with a lid. The samples were kept at room temperature, and examined as soon as possible, usually within two to four, sometimes six hours. Each sample was tested in respect of odour, pH and the number of *Bact. bifidum* present. In addition, cultures were made on endoagar and 2 per cent dextrose agar for purposes of comparison. As regards the determination of odour and pH, the former was always annotated first and the latter studied afterwards. This procedure was rigidly adhered to, in order that the examiner, in determining the odour, would not be influenced by the pH value.

The bacteriological procedure was as follows.

Approximately 1 to 2 g of faeces[1] was stirred carefully in a sterile mortar with sterile physiological saline solution. Dilution was done according to the following scheme with very vigorous shaking at each new stage of dilution. The pH was determined in a solution of 1:10 with an auto-ionometer with glass electrode.

From three of the final dilutions (see Fig. 1), *i.e.* $1 : 10^{-6}$ to

[1] OLSEN has demonstrated that nothing can be gained by proceeding from the dry substance (1949).

$1 : 10^{\pm 9}$, 1 ml is transferred to tubes containing, respectively, endoagar, 2 per cent dextrose agar, and tomato agar at a culture medium temperature of between 45 and 50° C. After careful mixing, the two first-named are poured into Petri dishes, while the tomato agar is allowed to jellify in the tubes. Incubation then takes place in a thermostat at 37° C; the tubes with tomato agar for three days, the others for 24 hours. The number of colonies is then counted in all the tubes and dishes. The dilution procedure is checked by comparing figures from the different dilutions in the same culture medium.

In addition, one of the tomato agar tubes containing a suitable number of colonies is examined in respect of the size of the colonies and their shape and distribution in the tube. (It may be mentioned that *Bact. bifidum* always leaves a free zone of about 1 cm at the surface.) The agar column is transferred to a sterile Petri dish. Ten colonies of varying size, appearance and position are cut out, and microscopic specimens and stab cultures then prepared from each. After Gram-staining, the samples are examined microscopically and the results compared with the respective random cultures. It is thus possible to ascertain whether the bacteria grow aerobically or anaerobically. The percentage of *Bact. bifidum* in these ten colonies is considered to be valid for the whole tube of tomato agar from which they are taken. A calculation is made of the number of *Bact. bifidum* in 1 g of faeces.

Error of Method

In estimating the error of method, double determinations were made on 20 samples of faeces from 18 infants. The samples represented the following forms of feeding: breast (4 samples); heated breast milk (7); supplemented breast feeding (4); cow's milk formula (1); and mixed diets (4). All phases of the method were duplicated and the two examinations were carried out within the space of 1 to $1\,^1/_2$ hours. The values obtained are shown in Table 1.

The statistical computation of the error of method was done in the following manner.

UNIVERSITY OF MICHIGAN LIBRARIES

Table 1

Double Determinations

No. of Sample	Diet	Sample	pH	Millions of Bacteria per 1 g of Faeces		
				Coliform	Growing on Dextrose Agar	Bact. Bifidum
485	Breast	I	5.2	200	230	22 000
		II	5.2	230	260	18 000
543	Breast	I	5.0	206	170	32 000
		II	5.0	163	142	37 000
569	Mixed	I	8.5	450	650	3 300
		II	8.5	580	670	4 000
573	Heated	I	5.4	1 560	1 940	11 900
	Breast Milk	II	5.4	1 650	1 600	12 600
604	Mixed	I	6.7	140	350	2 820
		II	6.7	70	380	3 710
612	Supplemented	I	6.1	28	49	8 200
	Breast	II	6.1	26	34	8 300
632	Supplemented	I	7.8	880	930	43 000
	Breast	II	7.8	1 020	960	25 000
659	Mixed	I	7.7	18	150	1 400
		II	7.7	43	128	1 050
679	Heated	I	5.3	1 160	1 110	20 000
	Breast Milk	II	5.3	702	1 270	25 000
692	Mixed	I	8.0	45	432	9 540
		II	8.0	46	394	8 380
997	Heated	I	6.5	490	1 870	70 000
	Breast Milk	II	6.7	170	2 160	80 000
1005	Breast	I	6.7	185	800	97 000
		II	6.7	395	1 140	75 000
1022	Supplemented	I	7.8	93	990	87 000
	Breast	II	7.8	57	620	70 000
1036	Supplemented	I	5.8	23	83	34 000
	Breast	II	5.8	12	85	29 000
1046	Heated	I	5.3	183	310	7 300
	Breast Milk	II	5.3	258	530	6 700

(Table 1 cont.)

No. of Sample	Diet	Sample	pH	Millions of Bacteria per 1 g of Faeces		
				Coliform	Growing on Dextrose Agar	Bact. Bifidum
1068	Half-Milk	I	8.3	1	30	135 000
	Formula +β-lactose	II	8.3	1	20	54 000
1073	Heated	I	5.8	174	278	9 800
	Breast Milk	II	5.8	72	179	6 500
1079	Heated	I	5.8	123	320	30 000
	Breast Milk	II	5.8	165	440	32 000
1101	Breast	I	5.6	< 1	12	16 500
		II	5.6	< 1	10	42 000
1105	Heated	I	5.7	580	850	4 400
	Breast Milk	II	5.7	500	600	4 700

The error of method in respect of the logarithmic values was calculated with the formula $s = \sqrt{\Sigma \frac{d^2}{2n}}$, where d is the logarithmic difference between a pair of double determinations and n is the number of such pairs.

The error of method in respect of the original values will then be $10^{\pm s}$. From this the conclusion can be drawn that the correct value lies, with 95 % confidence, in the interval $10^{\pm 2s}$.

This interval can be given most appropriately in per cent of the value obtained.

Coliform $n = 18$ $s = 0.16$; $10^{\pm 2 \cdot 0.16} = +110\,\%, -50\,\%$
Bacteria growing
on dextrose agar $n = 20$ $s = 0.085$; $10^{\pm 2 \cdot 0.085} = +\ 50\,\%, -30\,\%$
Bact. bifidum $n = 20$ $s = 0.112$; $10^{\pm 2 \cdot 0.112} = +\ 70\,\%, -40\,\%$

Thus the error of method is relatively small.

Discussion of the Method

With the aforegoing procedure for dilution, the weighed quantity of faeces was kept in physiological saline solution for

20—30 minutes and in distilled or sterilised water for 5—10 minutes. Distilled water was used in the early stages of the investigation, but subsequently replaced by sterilised water because it proved difficult to obtain sufficient quantities of water distilled in glass. The investigatory results were not affected by this change.

With regard to the degree of fineness of the faecal material it was found that nothing could be gained by further mashing, e.g. in a cylinder with a ground-in rotating glass rod. Samples were taken for culturing both before mashing of the material to an extra fine consistency and at regular intervals during the course of that process. No increase was found in the number of growing bifidum colonies, but on the other hand the number decreased if the mashing was continued too long.

The sterile saline solution used in the first stage of dilution was stored, after sterilisation, in a flask closed with a plug of cotton wool. To determine in what degree saline solution stored in this way may give the faecal emulsion a different pH value than may a recently boiled out carbon dioxide-free solution, comparative pH determinations were made in a number of cases taken at random. The significance of the degree of dilution for the pH of the faecal emulsion was investigated concurrently.

The pH, determined in a dilution of one part faeces to three parts newly boiled physiological saline solution, was found to be 0.2—0.3 lower than that in a dilution of one part to ten parts sterile physiological saline solution from stock. Hence the pH values given in the following are estimated to be about 0.2—0.3 higher than the true values.

CHAPTER I

Breast Feeding

Earlier Investigations

As already mentioned, TISSIER (1900), and following him a number of investigators, have been able to demonstrate qualitatively that *Bact. bifidum* dominates the faecal flora in breast-fed infants. This view has been verified by OLSEN (1949) in a quantitative bacteriological analysis of faeces. He investigated, for instance, regular samples of faeces in a number of infants from birth till the age of one year. In a review comprising one sample from each of nine breast-fed infants between the ages of ten days and three months, the bifidum count varied between 5 000 million and 400 000 million per gramme faeces. At the same time the number of coliform bacteria ranged between 0.01 million and 5 000 million per gramme, which values were not exceeded by certain other intestinal bacteria. Throughout the course of this investigation of breast-fed infants, bifidum counts lower than 10 000 million per gramme were obtained only sporadically. All of the samples had an acid odour and their pH was in most cases between 5.0 and 5.5, with upper and lower limits of 6.5 and 4.5.

During the first few days of life, *Bact. bifidum* occurs in varying, and often relatively low, numbers in purely breast-fed infants. For instance OLSEN (1949), on examining the faeces of four infants 4—5 days old, found the number was lower than 0.01 million in three of them, but about 7 000 million per gramme in the fourth. These samples had a marked acid odour and a pH of between 5.2 and 5.5.

Case Material

This consisted of 54 healthy infants fed solely on the breast from birth, who were either nursed in their homes or had been

UNIVERSITY OF MICHIGAN LIBRARIES

admitted to homes for healthy mothers with children. All of them were kept under medical supervision. A few were given 10 drops of concentrated cod liver oil daily; otherwise no additions to the diet occurred.

One sample of faeces was taken from each of 30 infants and 2—3 samples from each of 21 infants. In the remaining three a series of samples were taken over a period of 5 to 7 weeks.

Results

Since it is already clear from Olsen's investigation (see above) that the number of *Bact. bifidum* does not become stabilised until some time after birth, the eight samples that were taken prior to the tenth day of life are reported separately (Table 2).

Table 2

Breast-Fed Infants Under Ten Days

Age	Faeces		Millions of Bacteria per 1 g of Faeces		
	Odour	pH	Coliform	Growing on Dextrose Agar	Bact. Bifidum
4 days	A	4.4	< 1	< 1	24 000
4 »	»	5.3	4 300	4 400	< 100
5 »	»	4.8	< 1	< 1	6 600
5 »	»	5.0	163	142	37 000
6 »	»	5.0	4 410	6 900	< 100
6 »	»	5.8	2	5	17 000
7 »	»	4.9	252	148	25 000
9 »	»	4.9	140	178	11 700

The number of investigated breast-fed infants between the ages of 10 days and 5 months amounted to forty-six. One sample value from each of these infants is shown in Table 3. (In the case of infants examined several times, the second sample in the series is taken here.)

It is evident from Table 3 that the bifidum count in the tested samples varied from 1 100 million to 153 000 million per gramme, the mean value being 32 000 million. Ninety per cent

Table 3

Breast-Fed Infants

No. of Sample	Age	Faeces		Millions of Bacteria per 1 g of Faeces		
		Odour	pH	Coliform	Growing on Dextrose Agar	Bact. Bifidum
1067	1 month	A	5.8	39	100	1 100
513	2 »	»	5.5	1 210	1 270	2 000
892	1½ »	»	4.8	35	54	5 800
549	25 days	»	5.3	22	23	6 700
716	3 months	»	4.6	8	37	7 500
644	4 »	»	5.4	480	780	9 000
648	1 »	»	5.2	< 1	—	11 000
579	3½ »	»	5.5	750	107	11 790
1049	1½ »	»	5.3	400	910	15 000
1042	1 »	»	5.0	1 260	1 750	16 200
483	2½ »	»	5.2	40	120	19 800
347	1 »	»	5.4	< 1	< 1	20 000
589	1½ »	»	5.9	1 050	1 630	20 000
485	2½ »	»	5.2	200	230	22 000
539	24 days	»	5.1	< 1	< 1	22 000
1031	2 months	O	4.8	< 1	4	22 000
330	21 days	A	5.4	< 10	50	23 000
1030	3½ months	(F)	6.3	7	58	25 000
1051	24 days	A	5.0	372	510	25 000
311	2 months	»	5.4	220	290	30 000
698	2½ »	»	4.2	36	112	30 000
992	1 »	»	6.0	28	2	32 000
373	17 days	»	5.3	4 600	4 800	32 900
872	2½ months	»	6.1	117	1 060	35 000
876	16 days	»	5.1	124	690	35 000
761	2 months	»	5.0	< 1	8	40 000
480	3 »	F	5.9	300	600	40 000
677	2½ »	A	5.8	13	329	40 500
825	25 days	»	5.9	< 1	< 1	41 000
1059	> 1½ months	»	6.7	230	400	42 000
538	> 1½ »	»	5.9	500	350	46 000
342	21 days	»	5.8	210	280	51 000
994	1 month	»	7.6	170	3 140	52 000
664	2 »	»	7.2	< 1	1 690	54 000
599	2½ »	»	6.0	3	34	60 000

UNIVERSITY OF MICHIGAN LIBRARIES

(Table 3 cont.)

No. of Sample	Age	Faeces		Millions of Bacteria per 1 g of Faeces		
		Odour	pH	Coliform	Growing on Dextrose Agar	Bact. Bifidum
1017	26 days	A	5.0	< 1	< 1	61 000
540	24 »	»	5.0	122	115	65 000
313	4½ months	»	5.9	660	680	68 400
340	17 days	»	5.2	1 200	1 500	73 000
904	2½ months	F	6.9	308	2 820	81 000
717	1 »	A	5.4	10	8	84 000
965	22 days	»	6.3	306	530	85 000
344	2 months	F	8.3	510	580	115 000
336	3½ »	A	5.3	300	2 400	119 000
975	1 »	»	7.8	152	5 700	125 000
1018	1 »	»	4.9	470	530	153 000

of the values exceeded 10 000 million per gramme. The number of coliform bacteria and of bacteria growing on dextrose agar was below 6 000 million per gramme; in four cases both counts were less than 1 million per gramme. The mean value in respect of bacteria growing on dextrose agar was 160 million per gramme. No significant correlation existed between the number of *Bact. bifidum* and the number of other bacteria ($r = 0.16$, $P < 95\ \%$) (Fig. 2). In tomato agar only *Bact. bifidum* formed colonies as a rule. In most cases the samples had an acid odour; the pH was between 5.0 and 6.0 in 65 per cent, and between 4.5 and 6.5 in 80 per cent.

In Fig. 3 the logarithmic bifidum values from Table 3 are reproduced in relation to the respective ages.

To determine whether the number of *Bact. bifidum* and of other bacteria showed any tendency to change with increasing age, the series were divided into six different periods, so arranged that approximately equal numbers of values were obtained in each period. The mean value for each of these periods was then computed. Bacteria growing on dextrose agar (a). *Bact. bifidum* (b). Number of cases in respective periods (n).

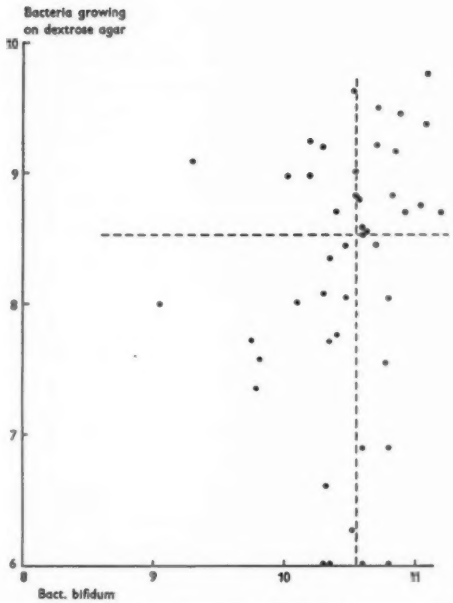


Fig. 2. Bifidum count in relation to number of bacteria growing on dextrose agar in 46 breast-fed infants aged from 10 days to 5 months (see Table 3). The broken line denotes the median of the respective variables.

Days	15—22	23—30	31—45	46—70	71—85	86—135
(a)	8.8	7.4	8.3	8.3	8.5	8.4
(b)	10.7	10.4	10.4	10.5	10.6	10.4
(n)	6	9	9	8	8	6

Since no significant difference can be demonstrated between the respective periods, the latter will therefore be pooled, the resultant values being as follows:

(a) $n = 45 \quad \bar{x} = 8.2 \pm 0.16$
(b) $n = 46 \quad \bar{x} = 10.5 \pm 0.065$

In Fig. 3, the mean bifidum counts in respect of the six different periods are signified by dots, which have been linked up with each other. In the following diagrams the continuous line

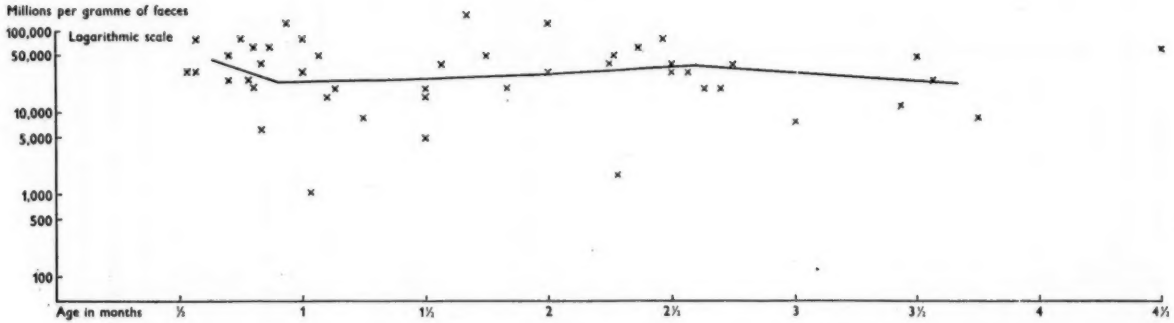


Fig. 3. Breast-fed infants. Bifidum count in relation to age in 46 infants aged from 10 days to 5 months (see Table 3). One value from each infant. The continuous line connects mean values in respect of different periods (see page 25).

Table 4

Breast-Fed Infants Submitted to Serial Tests

Date	Faeces		Millions of Bacteria per 1 g of Faeces		
	Odour	pH	Coliform	Growing on Dextrose Agar	Bact. Bifidum
E. M. Born 17.4.50					
3.5	A	5.1	124	690	35 000
15.5	»	6.6	5	126	27 000[1]
1.6	»	7.2	403	2 740	89 000
S. F. Born 22.6.49					
3.9	F	7.4	480	680	—
16.9	»	5.9	300	600	40 000
17.9	»	6.4	470	720	40 000
28.9	»	8.0	580	850	110 000
G. B. Born 5.8.50					
11.9	A	5.0	990	930	17 000
20.9	»	5.3	400	910	15 000
29.9	»	5.7	277	700	15 000
J. S. Born 10.8.50					
12.9	A	< 5.0	< 1	< 1	23 000
27.9	»	6.7	230	400	42 000
S. H. Born 4.8.49					
16.9	F	5.9	2 490	3 000	53 000
17.10	A	5.5	1 210	1 270	2 000
B. H. Born 10.1.50					
15.2	A	5.1	< 1	< 1	5 500
15.3	»	5.0	< 1	8	40 000
11.5	»	5.0	80	770	40 000
G. S. Born 26.3.50					
8.5	A	4.8	35	54	2 000
24.5	»	5.0	9	259	5 800
A. S. Born 15.10.49					
17.12	A	7.1	10	40	7 200
6.2.50	»	5.4	480	780	9 000

[1] Somewhat too low due to fault in culture medium.

UNIVERSITY OF MICHIGAN LIBRARIES

obtained in this way represents the breast-fed series with respect to bifidum count.

To illustrate the findings in one and the same infant at different examinations, some of the cases tested twice or more are reviewed in Table 4. This table indicates that certain infants presented a constantly high and others a constantly low bifidum count, whereas others again showed major variations. Infant G. Q. presented a distinct increase with mounting age. None of these children had any infection on examination except E. O., who had a slight throat infection during the follow-up period, but was clinically symptom free on June 28 at the latest.

Summary

The investigation has shown that in a series of 46 healthy breast-fed infants between the ages of 10 days and 5 months the bifidum count varied between 1 100 million and 153 000 million per gramme, the mean value being 32 000 million. Ninety per cent of the values exceeded 10 000 million per gramme. Some of the children underwent a series of two to five tests over a period of up to 5—7 weeks. Some of them showed a continuously low and others a continuously high bifidum count, and others again very great variations without presenting any clinical symptoms of disease. Further, the number of *Bact. bifidum* was not demonstrably correlated either to that of other bacteria or to the age.

The number of other bacteria varied between < 1 million and 6 000 million per gramme faeces, with a mean value of 160 million for bacteria growing on dextrose agar. In 65 per cent of the cases the pH was between 5.0 and 6.0, with variations in both directions. In the main the faeces had an acid odour.

CHAPTER II

Feeding on Heated Breast Milk

Earlier Investigations

No quantitative investigation has earlier been conducted into the bifidum flora in infants fed on heated breast milk. Several investigators have sought, however, to elucidate problems in this field by microscopic studies of faecal specimens, but they have arrived at divergent views.

EPSTEIN and JELINEK (1932) and EPSTEIN (1933) found that breast feeding is not equivalent to feeding with expressed breast milk, and that in the latter instance the bifidum count will often be lower. RITSCHEL (1947—48), on studying premature infants fed on breast milk pasteurised at 65° C for 30 minutes, found "a beautiful bifidum flora" which in his opinion justified the conclusion that with respect to quality such breast milk is equal to untreated milk. KRISTEN and PETUELY (1950) investigated the relevant conditions mainly in premature infants by making regular tests over a period of several weeks. They found that expressed breast milk, pasteurised (at 65° C for 30 minutes) or sterilised (at 100° C for 8 minutes), when 12 hours old produced on the average a poorer bifidum flora than unheated breast milk refrigerated for some time. This breast milk in turn produced a poorer bifidum flora than that found in direct breast feeding. The investigators were not able to observe any significant difference between the pasteurised and the sterilised breast milk.

Case Material

This series consisted of clinically symptom-free infants, some of them full term and some premature, nursed mainly at the Sachs Hospital for Children or the Maternity Department of Södersjukhuset. The full-term infants could not be breast-fed for various reasons; in most cases because of tuberculosis in the

UNIVERSITY OF MICHIGAN LIBRARIES

mothers, but in a few because of injuries or maldevelopments in the central nervous system. All of the premature infants were nursed at the premature unit of the hospital, and presented no signs of disease apart from their congenital debility.

Most of the breast milk used in feeding these infants was supplied by the Breast Milk Bank in Stockholm. Such milk is pasteurised at 68° C for 10 minutes and then stored in a refrigerator, except for 3—4 hours during conveyance to the hospital. It is about 48 hours old when fed to the infant. To a minor extent expressed breast milk was obtained from the infants' own mothers or from other lactating women. This breast milk was stored in a cool place after being obtained, and in most cases was 4—20 hours old on delivery to the hospital. It was brought to the boil and thereafter kept in a refrigerator.

All the experimental infants, with a few specially indicated exceptions, were fed from birth on this heated breast milk. They received nothing else by mouth with the exception of vitamin D in concentrated form. In the majority of cases either one or two samples of the faeces were taken. In addition, eight full-term and seven premature infants underwent a series of tests over a period of 1—2 $^1/_2$ months. [Seven of these eight full-term infants were subsequently used as experimentees in determining the susceptibility of *Bact. bifidum* to antibiotics *in vivo* (see Chapter VII).]

Early Results

This investigation comprised 35 full-term and 23 premature infants. A total of 12 were younger than 10 days (Table 5); of the others 28 were full-term (Table 6 and Fig. 5) and 18 prematures (Table 7 and Fig. 6). Each infant is represented by one test only, the first in a series where such occurred.

As will be seen from Table 5, the bifidum count varied considerably in infants under 10 days, just as was the case in the breast-fed infants. Hence it is justified to exclude them from the case material as a whole.

Table 6 shows that the bifidum count in full-term infants, mainly up to the age of one month, varied between 240 million

Table 5

Infants Under Ten Days Fed on Heated Breast Milk

Age	Birth Weight (g)	Faeces		Millions of Bacteria per 1 g of Faeces		
		Odour	pH	Coliform	Growing on Dextrose Agar	Bact. Bifidum
Full Term						
5 days		A	5.4	60	460	1 200
7 »		»	5.3	1 290	1 310	2 100
7 »		»	5.1	1 400	1 490	3 690
7 »		»	4.7	242	305	4 000
8 »		»	5.3	160	205	126
8 »		»	5.3	7 600	9 200	720
9 »		»	6.3	2 420	3 330	< 100
9 »		»	5.7	540	720	4 550
Prematures						
6 days	1 900	A	6.3	450	8 300	< 100
8 »	2 250	»	6.0	2 960	3 800	< 100
9 »	1 190	»	5.9	4 600	8 400	960
9 »	1 230	»	5.1	2 980	3 480	5 500

and 25 000 million per gramme faeces. All values except two (93 per cent) were lower than 10 000 million, the mean value being 3 200 million per gramme. The number of other bacteria at the same time varied between 20 million and 7 600 million per gramme, with a mean value of 800 million in respect of bacteria growing on dextrose agar.

The faeces had an acid odour in all save two cases. The pH was between 5.0 and 6.0 in 80 per cent, and between 4.5 and 6.5 in 96 per cent of the cases.

Table 7 shows the corresponding findings in the premature group. Here the bifidum count ranged between 170 million and 15 500 million per gramme, all values except one (94 per cent) being below 10 000 million per gramme. The mean value was 2 500 million. The number of other bacteria varied between 90 million and 10 000 million per gramme, the mean value being

UNIVERSITY OF MICHIGAN LIBRARIES

Table 6

Full-Term Infants Fed on Heated Breast Milk. Age Ten Days to about One Month

No. of Sample	Age	Faeces		Millions of Bacteria per 1 g of Faeces		
		Odour	pH	Coliform	Growing on Dextrose Agar	Bact. Bifidum
812	15 days	A	5.3	310	760	240
466	10 »	»	5.3	4 100	5 400	500
653	19 »	»	5.2	1 940	2 520	800
554	25 »	»	5.1	940	1 470	980
734	8 weeks	»	5.2	102	1 140	1 320
638	10 days	»	5.2	1 730	1 930	1 500
1076	23 »	F	5.6	140	430	1 800
568	19 »	»	6.3	5 500	7 600	1 800
605	17 »	A	6.6	100	200	1 890
392	17 »	»	5.4	600	710	2 000
627	26 »	»	6.7	1 730	2 310	2 700
962	20 »	»	5.7	860	2 080	3 150
491	*	»	4.9	50	50	3 500
811	15 »	»	5.1	2 140	1 860	3 600
266	12 »	»	5.0	2 170	2 290	4 000
610	11 »	»	4.5	87	76	4 100
645	5 weeks	—	6.5	580	810	4 230
459	10 days	A	5.3	20	30	4 300
806	20 »	»	5.0	456	600	4 680
572	16 »	»	5.1	30	100	5 500
719	7 weeks	»	5.2	106	91	6 000
602	4 »	»	5.3	1 450	1 370	6 020
390	10 days	»	5.5	560	670	6 840
1046	24 »	»	5.3	221	420	7 000
454	4 weeks	»	—	750	770	7 600
488	*	»	5.5	740	770	9.500
575	14 days	»	5.8	930	930	20 000
1097	21 »	»	5.5	440	690	25 000

* Three-month-old breast-fed infants, given heated breast milk during the preceding two weeks.

Table 7

Premature Infants Fed on Heated Breast Milk. Age Ten Days to about One Month

No. of Sample	Age	Birth Weight (g)	Faeces		Millions of Bacteria per 1 g of Faeces		
			Odour	pH	Coliform	Growing on Dextrose Agar	Bact. Bifidum
830	17 days	1 590	A	5.0	560	1 780	170
839	5 weeks	1 280	»	5.4	980	980	735
931	4 »	1 400	»	5.7	1 420	1 430	1 040
691	22 days	2 110	»	5.3	5 740	8 300	1 215
625	6 weeks	1 850	»	5.3	2 800	2 600	1 316
555	19 days	2 080	»	5.3	90	590	1 400
1096	26 »	1 640	F	5.8	2 930	4 500	2 070
658	14 »	2 190	A	5.2	1 350	1 300	2 300
677	18 »	2 400	»	5.0	408	445	2 320
922	26 »	1 550	»	5.4	720	1 470	2 520
858	13 »	1 930	»	5.1	1 980	2 400	3 000
853	19 »	2 450	»	5.3	766	1 240	3 200
919	15 »	2 120	»	4.9	10 500	8 400	5 000
1034	4 weeks	1 200	»	4.9	305	590	5 800
620	22 days	1 950	»	5.2	4 800	3 400	6 570
684	18 »	2 060	»	5.1	146	162	7 200
683	25 »	1 360	»	5.1	199	169	7 200
588	12 »	2 430	»	6.3	2 250	2 470	15 500

1 300 million in respect of bacteria growing on dextrose agar. The faeces had an acid odour in all save one case. The pH was between 5.0 and 6.0 in 83 per cent, and between 4.5 and 6.5 in all of the cases.

There was no significant correlation between the number of *Bact. bifidum* and that of other bacteria either in the prematures or in the full-term infants ($r = -0.18$ and -0.30 respectively, $P < 95\,\%$ in both cases) (see Tables 6 and 7 and Fig. 4). The non-significant result may, however, be due to the small number of cases, and it seems not unlikely that the two numbers are slightly negatively correlated. In the tomato agar, other bacteria besides bifidum (chiefly gram-positive cocci)

UNIVERSITY OF MICHIGAN LIBRARIES

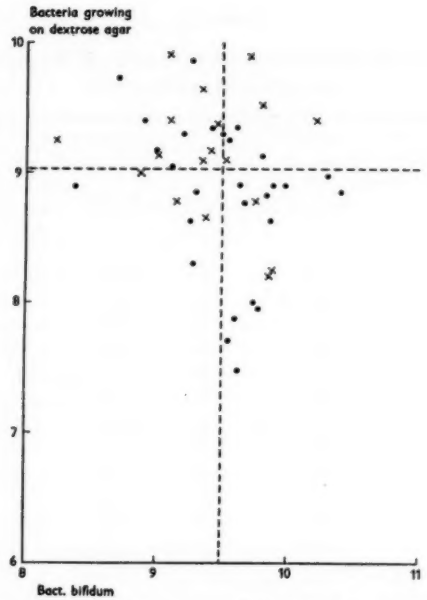


Fig. 4. Bifidum count in relation to number of bacteria growing on dextrose agar in 46 infants aged from 10 days mainly to 1 month, fed on heated breast milk (see Tables 6 and 7). Logarithmic scale. The broken line denotes the median of the respective variables. Full-term (•), premature (×) infants.

showed growth in roughly one-half of the cases, and more often in the prematures than in the full-term infants.

Figs. 5 and 6 show the distribution of bifidum values in each group in relation to the respective ages. In both instances we find an even distribution; there is no tendency to any change with increasing age during the period to which the series relates (mainly the first month of life).

The full-term and the premature infants fed on heated breast milk were compared with respect to the number of *Bact. bifidum* (b) and that of other bacteria, represented here by bacteria growing on dextrose agar (a).

	Full term	Premature	Difference
(a)	$n = 28$ $\bar{x} = 8.8 \pm 0.11$	$n = 18$ $\bar{x} = 9.1 \pm 0.12$	0.3 ± 0.16
(b)	$n = 28$ $\bar{x} = 9.5 \pm 0.084$	$n = 18$ $\bar{x} = 9.4 \pm 0.11$	-0.1 ± 0.14

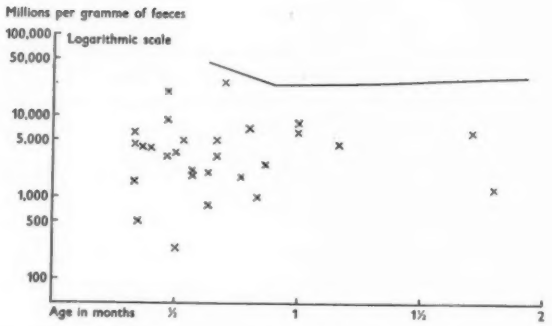


Fig. 5. Full-term infants fed on heated breast milk. Bifidum count in relation to age in 26 infants aged from 10 days mainly to 1 month (see Table 6). One value from each infant. The continuous line connects the group means of bifidum counts in the breast-fed infants (see Fig. 3).

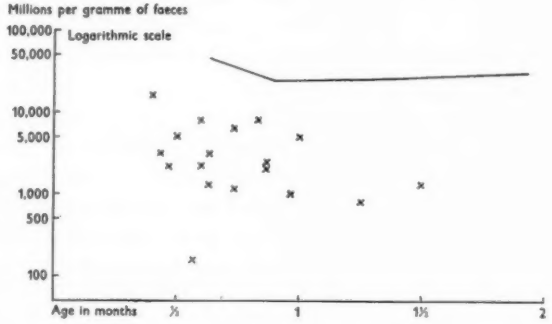


Fig. 6. Premature infants fed on heated breast milk. Bifidum count in relation to age in 18 infants aged from 10 days mainly to 1 month (see Table 7). One value from each infant. The continuous line connects the group means of bifidum counts in the breast-fed infants (see Fig. 3).

Since no significant difference exists, the groups can be combined and treated as one unit.

(a) $\bar{x} = 9.0 \pm 0.084$
(b) $\bar{x} = 9.5 \pm 0.066$

In order to study under more exact experimental conditions the significance of heating (boiling) relative to the bifidum-stimu-

Table 8

Infants Alternately Fed at Mother's Breast and on Boiled Breast Milk

Date	Faeces		Millions of Bacteria per 1 g of Faeces			Diet
	Odour	pH	Coliform	Growing on Dextrose Agar	Bact. Bifidum	
	E. T. Born Febr. 2					
28.2	A	5.7	120	600	25 000	Breast
1.3	»	5.8	210	280	51 000	
3.3	F	7.2	660	1 190	69 000	
7.3	A	5.2	1 700	1 800	10 700	Boiled breast milk from
8.3	»	5.7	5 300	6 400	3 330	mother 4.3–9.3
9.3	»	5.7	8 500	8 900	1 800	
14.3	A	4.7	< 1	< 1	12 000	Breast
17.3	»	4.9	< 1	< 1	16 000	
26.3	»	5.9	12	15	56 000	
	B. A. Born Febr. 10					
22.2	A	5.2	1 100	1 300	46 000	Breast
25.2	»	5.2	1 200	1 500	73 000	
1.3	»	5.3	170	340	80 000	
8.3	A	5.2	80	170	23 000	Boiled breast milk from
10.3	»	5.3	50	250	21 000	mother 4.3–10.3
18.3	A?	6.5	< 1	< 1	79 000	Breast
19.3	F	5.1	123	163	54 000	

lating property of breast milk, the following investigation was conducted. Two clinically symptom-free breast-fed infants with no supplementary food, living in an infection-free environment, were fed for one week on fresh boiled breast milk. The mothers had expressed the milk from the breast before each meal and then brought it to the boil before feeding it to the infants. A number of samples of faeces were examined before, during and after the week in question. The results are shown in Table 8.

It is evident from the above table that during the period in which they were fed on boiled breast milk, both infants showed

Table 9

Infant Changed from Feeding on Heated (Pasteurised) Breast Milk to Direct Breast Feeding

Date	Faeces		Millions of Bacteria per 1 g of Faeces		
	Odour	pH	Coliform	Growing on Dextrose Agar	Bact. Bifidum
Fed on Heated Breast Milk for Preceding Two Weeks					
26.9	A	4.9	50	50	3 800
Breast Feeding since 27.9					
5.10	(F)	6.7	139	2 120	180 000
12.10	A?	6.9	340	480	92 000

a substantially lower bifidum count than that occurring in breast feeding before and after that period. In the case of infant E. T. the decrease was very pronounced (> 90 per cent), and at the same time there occurred a substantial increase in the number of other bacteria. The bacterial count in the three groups returned to the ordinary values for breast-fed infants as soon as direct breast feeding was resumed. In the case of infant B. A., the decrease in the bifidum count amounted to 50—75 per cent, which lies beyond the limits of error of the method (see page 19). In this case the number of other bacteria showed no change during the course of the experiment. The pH in both cases was at a more or less constant level. During the week of the experiment the infants' stools presented no unequivocal alterations in appearance, odour and number.

The change in the bifidum flora on transition from feeding with heated (pasteurised) breast milk to direct breast feeding is further illustrated by the following investigation. An infant of three months who spent two weeks in the hospital, symptom-free following an acute intestinal infection, during which period it received heated (pasteurised) breast milk only, was fed solely on the breast after its discharge. Samples of the faeces before and after this change (see Table 9) showed an exceptionally

UNIVERSITY OF MICHIGAN LIBRARIES

Table 10

Comparison between the Effect on the Faeces of Boiled and of Pasteurised Breast Milk

Age	Faeces		Millions of Bacteria per 1 g of Faeces		
	Odour	pH	Coliform	Growing on Dextrose Agar	Bact. Bifidum
Boiled Breast Milk					
11 days	A	5.3	< 1	< 1	2 500
12 »	»	5.0	2 170	2 290	4 000
25 »	»	5.1	940	1 470	980
4 weeks	»	—	750	770	7 600
Pasteurised Breast Milk					
11 days	A	4.5	87	76	4 100
16 »	»	5.1	30	100	5 500
23 »	F	5.0	140	430	1 800
4 weeks	A	5.1	66	11	3 300

pronounced increase in the bifidum count. The reason for the observed rise in the pH level could not be determined.

Some of the results from Table 6 are reproduced in Table 10 to show the comparative significance of boiling and pasteurisation of breast milk with respect to the bifidum flora. The figures relate to infants who were fed solely on the respective types of heated milk from birth. It is evident that no difference in principle existed in this series.

Late Results

The eight full-term infants from whom a series of samples was taken were fed on pasteurised breast milk from the Breast Milk Bank. The only exception is infant S. H., who was fed, during the first two months of the experimental period, on boiled breast milk which the mother had forwarded to the hospital. The results of the examinations of faeces will be found in Tables 11 and 27. Fig. 7 shows the bifidum counts in the followed up series of eight infants.

Table 11

Full-Term Infant Fed on Heated Breast Milk (F. H. Born 19.5)

Date	Faeces		Millions of Bacteria per 1 g of Faeces		
	Odour	pH	Coliform	Growing on Dextrose Agar	Bact. Bifidum
8.6	A	5.7	860	2 080	3 150
15.6	»	5.1	66	11	3 300
21.6	F	6.6	320	2 000	75 000
28.6	(A)	6.3	53	131	7 800
12.7	A	4.4	7	6	82 000

As will be seen from Tables 11 and 27 the bifidum count in the eight experimentees, during the prolonged feeding on heated breast milk until the first period of treatment with antibiotics, rose consistently from initial values between about 1 000 million and 10 000 million up to values between 10 000 million and 100 000 million per gramme faeces. The increase was not continuous but showed substantial variations in the bifidum values. Only when the upward trend had ceased did the values remain relatively stationary at the new level. No correlation was found between these changes and the variations in that part of the other faecal flora that was investigated. After the age of six weeks the pH values showed a wider dispersion; they had previously varied between 4.9 and 6.6, but then between 4.2 and 7.6.

From Fig. 7, in which are reproduced the bifidum values from Tables 11 and 27 prior to treatment with antibiotics, the following conclusions can be drawn. During the two months covered by this part of the investigation, the bifidum count in the eight experimentees rose from values mainly below 10 000 million between the ages of 2 and 6 weeks, to values largely above 10 000 million per gramme between the ages of 6 and 10 weeks.

With a view to investigating the effect of expressed unheated breast milk on the bifidum flora in this stage, five infants were fed on such milk for periods varying between 5 and 12 days.

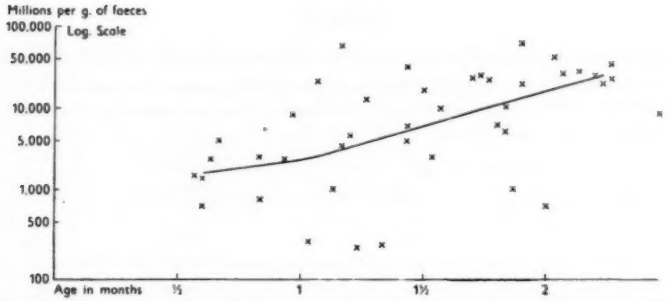


Fig. 7. Bifidum counts in follow-up series of 8 full-term infants fed on heated breast milk. No other food and no medicinal treatment was given during the course of the experiment. The continuous line connects mean values in respect of different periods.

Two of them (S. H. and Å. Z.) received breast milk that was 6 to 40 hours old at the time of feeding, while three (M. H., Å. S. and M. O.) largely received milk 4 to 12 hours old. According to PETUELY and KRISTEN (1950) the bifidum-stimulating capacity of breast milk declines when it is stored.

The results were not uniform. In infant Å. Z., the unboiled breast milk occasioned a substantial though transient fall in the bifidum count. This change occurred without any clinical symptoms of intestinal disorder or without any demonstrable reaction in the bacterial conditions recorded here. An increase in the bifidum count occurred in the other cases, but it was not of such magnitude as to have been attributable with certainty to the changeover to unboiled breast milk. Due to the small number of cases, no tests of significance were made on the bifidum counts described in this section.

The premature infants from whom serial samples were taken had been fed both on boiled and on pasteurised breast milk. The results of the examinations of faeces are shown in Table 12. It will be seen that the bifidum count, as in the full-term infants, progressively increased, though with less regularity. In certain infants the rise was faster, in others slower, than the average in the full-term infants. In a few of them there was still no demonstrable tendency to increase after seven weeks; these included a pair of twins.

Table 12

Premature Infants Fed on Heated Breast Milk, Submitted to Serial Tests

Date	Faeces		Millions of Bacteria per 1 g of Faeces		
	Odour	pH	Coliform	Growing on Dextrose Agar	Bact. Bifidum
G. S. Born Apr. 4. Birth weight 2 240 g					
22.4	A	6.0	2 960	3 850	100
17.5	»	5.2	1 820	2 390	45 000
20.5	»	4.0	52	124	28 000
2.6	»	5.9	1 860	3 090	87 000
A. T. Born Jan. 31. Birth weight 2 110 g					
22.2	A	5.3	5 470	8 300	1 200
27.2	»	5.0	1 910	2 900	13 000
8.3	»	5.7	264	296	58 000
16.3	»	5.1	182	920	54 000
G. N. Born Jan. 25. Birth weight 1 360 g					
20.2	A	5.1	199	169	7 200
27.2	»	5.4	60	310	145
6.3	»	5.2	575	483	400
15.3	»	4.5	55	122	14 000
B. Tw. I. Born Apr. 24. Birth weight 1 550 g					
20.5	A	5.4	720	1 470	2 500
27.5	»	5.4	480	820	246
17.6	»	4.7	1 070	1 020	4 500
4.7	»	4.5	31	19	—
13.7	(F)	5.7	210	740	6 300
B. Tw. II. Born Apr. 24. Birth weight 1 400 g					
23.5	A	5.7	1 420	1 430	1 040
30.5	»	5.9	—	—	1 610
10.6	»	5.7	1 560	3 150	550
15.6	»	5.2	36	4	1 320
30.6	»	4.2	80	12	16 000
12.7	»	4.3	2	2	23 000

(Table 12 cont.)

Date	Faeces		Millions of Bacteria per 1 g of Faeces		
	Odour	pH	Coliform	Growing on Dextrose Agar	Bact. Bifidum
E. Tw. I. Born Apr. 4. Birth weight 1 190 g					
20.4	A	5.9	4 600	8 400	960
28.4	»	5.2	—	1 190	9 000
16.5	»	5.2	2 230	—	150
23.5	O	5.6	3 520	3 760	34
30.5	A	5.3	1 460	1 940	3 000
9.6	»	5.4	180	670	1 200
E. Tw. II. Born Apr. 4. Birth weight 1 230 g					
20.4	A	5.1	2 980	3 480	5 500
28.4	»	5.9	1 740	4 780	665
6.5	O	5.3	2 550	5 820	210
16.5	A	5.5	1 420	2 930	51
23.5	»	5.5	3 160	2 900	—
30.5	»	5.2	—	—	200
9.6	»	5.7	1 140	1 940	1 560

Clinical Observations

The eight experimentees were followed up during the course of five to seven weeks feeding solely on heated breast milk without any form of medicinal treatment. Clinically no distinction could be made during that period between these infants and ordinary breast-fed infants; they were well in all respects. The weekly increase in weight averaged between 130 and 220 grammes. Regurgitation scarcely occurred at all, and the infants had good appetites. Defaecation occurred two to four times a day up to a body weight of 3.6—3.9 kg, whereafter it fell to 0—2 per day. In appearance the stools resembled those of breast-fed infants, and at the outset they all showed a low pH and an acid odour. Between the ages of 1 $^1/_2$ and 3 $^1/_2$ months the pH rose in four of the infants to values around or over 7, the odour concurrently changing to faecal in each case. No change was observed in the faeces which could be correlated to the increase in the bifidum count.

An exception to the above was infant S. H., whose weight rose by only 220 g in the course of seven weeks observation. However, this infant was suffering from internal hydrocephalus, and received only such milk as was expressed by the mother, the quantity manifestly being too small. The stools became regular, somewhat porous and often formed, in conjunction with a rise in the pH and a change to faecal odour. It is worthy of note that these changes in the pH and odour occurred while the number of *Bact. bifidum* was on the increase.

Summary

This investigation showed that in a series consisting of 28 full-term and 18 premature infants, mostly between the ages of 10 days and 1 month, and fed on heated breast milk since birth, the bifidum count varied between 170 million and 25 000 million per gramme faeces, the mean value being 3 200 million per gramme. In 93 per cent the values were below 10 000 million per gramme. The number of other bacteria at the same time varied between 20 million and 10 000 million per gramme, with a mean value of 1 000 million in respect of bacteria growing on dextrose agar. No correlation could be demonstrated between the number of bifidum and that of other bacteria. In the aforegoing respects no difference existed between the full-term and the premature infants.

Eight of the full-term and seven of the prematures were followedup during the course of continued feeding on heated breast milk. In the full-term infants the bifidum count progressively increased during the first and second months, and reached values between 10 000 million and 100 000 million per gramme. No correlation was found between these changes and the variations in that part of the other faecal flora that was investigated. The bifidum count rose in the premature infants too, though in a less regular way. In some of them the increase was faster, in others slower, than the average in the full-term infants. A few of them still showed no tendency to increase after seven weeks.

In the entire series the pH varied between 5.0 and 6.0 in 80 per cent and was below 7 in all cases. In the main the faeces

had an acid odour. In four of the full-term infants who were observed during the course of continued feeding on heated breast milk, the pH rose to values around or over 7 between the ages of 1 $^1/_2$ and 2 $^1/_2$ months. Concurrently there was a regular change from acid to faecal odour. These changes showed no tendency towards spontaneous regression.

CHAPTER III

Bottle Feeding

Earlier Investigations

The investigations hitherto conducted into the occurrence of *Bact. bifidum* in bottle-fed infants have given rise to extremely divergent views. It had earlier been considered for a time that breast milk was an essential requisite for the presence of *Bact. bifidum* in the intestines and that the microorganism disappeared when bottle feeding succeeded breast feeding. BLAUROCK (1937) and others, verifying the results published by TISSIER (1900) prior to the above findings, showed that *Bact. bifidum* also occurs normally in bottle-fed infants, though in much smaller numbers than are found in breast-fed infants. According to these investigators, *Bact. bifidum* loses completely its predominant position in the faecal flora of breast-fed infants as soon as they change to bottle feeding.

More recently OLSEN (1949), by quantitative bacteriological analyses of faeces from infants, has arrived at the conclusion that the faeces of breast-fed and of bottle-fed infants show no statistically significant difference with respect to the bifidum count. OLSEN was able to observe, however, that the majority of breast-fed infants had a somewhat higher count than the majority of bottle-fed infants. His comparative series consisted of 13 breast-fed and 15 bottle-fed infants between the ages of 4 days and 3 months.

Case Material

Since the vast majority of Stockholm children are born in maternity departments, and in general are fed on breast milk there, the present series includes only one child (L. B.) that was entirely bottle-fed from birth. The remainder of the investigated infants were, in the beginning, fed either at the breast or on

heated breast milk, in both cases supplemented by bottle feeding for varying periods. The period as a bottle-fed infant has been counted as from the first day of feeding on the bottle alone.

The investigation comprised 34 of these bottle-fed infants. All of them were full term, clinically symptom free, and were not over the age of 6 months. Some of them were nursed in their own homes, others in children's homes, and a very small number at the Sachs Hospital for Children. In 13 cases the infants received citric acid milk, and in 21 cases half-milk formula. The addition of vitamin D in the form of concentrated cod liver oil was compulsory. A few of the oldest children were given small quantities of fruit juice, but otherwise the diet in no case was supplemented. In 24 of the infants, either one or two samples were taken of the faeces, while in 10 a series was taken over periods of 2 weeks to 3 months.

Results

The series comprising bottle-fed infants is shown in Table 13, in which group 1 comprises infants given citric acid milk and group 2 infants given half-milk formula. Each infant is represented by only one test, this being the second one in cases where serial samples were taken. With two exceptions (595 and 596) the samples were taken two weeks at the earliest after the start of bottle feeding alone. The two exceptions had previously been virtually bottle-fed infants for several weeks, since they received during that period heated breast milk in such small quantities (100—150 g per day) that in this context it can be quite overlooked.

As will be seen from Table 13, the bifidum values ranged from < 100 million to 28 000 million per gramme, the mean value being 4 000 million. Seventy-five per cent of the values were below 10 000 million per gramme. The variation in the values was the same in both groups. In tomato agar, four-fifths of the cases showed varying growths of other bacteria (chiefly gram-positive cocci) in addition to *Bact. bifidum*. The mean value in respect of bacteria growing on dextrose agar was 1 600 million per gramme. The number of bifidum did not appear to be cor-

Table 13

Bottle-Fed Infants

No. of Sample	Age	Entirely Bottle-Fed for Period of	Faeces		Millions of Bacteria per 1 g of Faeces		
			Odour	pH	Coliform	Growing on Dextrose Agar	Bact. Bifidum
Group 1. Citric Acid Milk							
592	4 months	6 weeks	F	8.8	5 800	6 400	1 500
1021	3 weeks	3 »	»	7.1	3 400	2 500	1 760
760	3½ months	3 »	»	8.2	38	3 400	1 880
600	1½ »	6 »	»	8.4	6 100	8 000	2 880
999	3½ »	4 »	»	8.2	640	710	4 400
859	1½ »	4 »	»	7.0	23	2 450	4 770
595	3 »	1 »	»	8.6	300	530	4 800
764	2 »	3 »	»	8.1	266	18 300	4 800
1043	1½ »	4 »	»	6.2	4 000	4 300	5 700
784	3½ »	5 »	»	7.9	430	620	6 500
1019	1½ »	6 »	»	7.3	1 010	2 130	10 200
1094	5 »	3 »	»	6.8	1 160	3 700	14 000
1093	5½ »	8 »	»	6.9	320	720	16 000
Group 2. Half-Milk Formula							
827	3 months	7 weeks	F	8.0	1 150	1 400	< 100
980	3 »	6 »	»	7.7	1 400	1 200	< 100
607	3 »	4 »	»	8.1	940	123	250
826	2½ »	2½ months	»	7.9	2 250	3 680	480
837	3½ »	3 »	»	7.8	218	950	1 200
832	3½ »	1 »	»	6.8	690	1 360	1 390
768	3½ »	3 »	–	8.0	5 000	6 700	1 450
598	4 »	1½ »	F	7.8	60	290	1 750
788	1 »	2 weeks	»	7.0	210	2 280	2 500
596	3 »	1 »	»	7.3	247	416	3 200
617	3 »	1½ months	»	5.1	2	13	3 900
1004	2½ »	1½ »	»	7.9	700	220	4 140
869	3 »	2 »	»	5.8	850	5 800	5 440
958	3 »	1 »	»	7.9	474	1 080	9 540
312	2½ »	2 »	»	8.7	760	760	9 600
1026	3 »	1 »	»	8.6	1 210	2 400	9 600
767	4 »	2 »	»	7.8	255	15 800	14 400
705	3 »	2 »	»	8.5	12	6 500	15 210
1081	1 »	3 weeks	»	6.7	3 200	3 900	16 200
1069	3 »	7 »	»	8.3	191	347	28 000
1062	1½ »	4 »	»	7.8	940	3 200	28 000

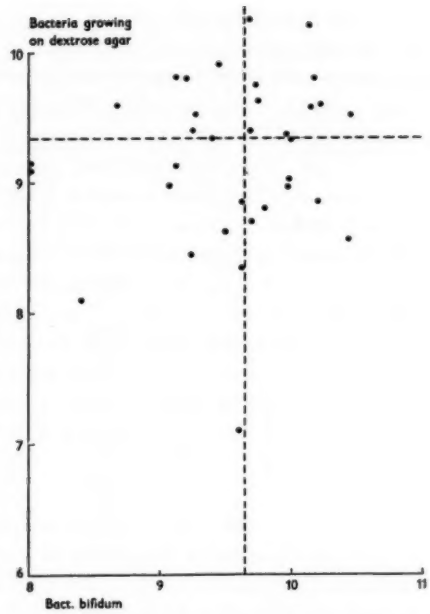


Fig. 8. Bifidum count in relation to number of bacteria growing on dextrose agar in 34 bottle-fed infants aged from 3 weeks to 5 months (see Table 13). Logarithmic scale. The broken line denotes the median of the respective variables.

related to that of other bacteria ($r = 0.14$, $P < 95$ %) (Fig. 8). The odour was consistently faecal and, with a few exceptions, the pH values were higher than seven.

In Fig. 9 the logarithmic values for the bifidum count are reproduced from Table 13 in relation to the period in which the infant was entirely bottle-fed. Origo corresponds to the first day of bottle feeding alone. The bifidum values show an even distribution in relation to time; there is no tendency towards any change with increasing age.

To illustrate further the conditions in one and the same infant over a period of several months solely on bottle feeding, seven full-term infants between the ages of 2 weeks and 6 months were

submitted to serial tests. Samples were taken two to three times per month. If any upper respiratory tract infection occurred, a safe interval was always allowed before the next sample was taken. One case (infant L. B.) is reported separately, the other results being shown in Table 14 and Fig. 10. To facilitate a survey, however, only four infants have been included in the latter diagram.

Table 14 and Fig. 10 show full concordance with the results reported above (Table 13). The bifidum count occasionally exceeded 10 000 million per gramme, and otherwise varied between 100 million and 31 500 million per gramme. There was no demonstrable tendency towards any rise with increasing age. As regards other bacteria, nothing emerged beyond the observations that have already been made.

The only infant (L. B.) in the series who at no time received breast milk (Table 15) was fed from birth on half-milk formula, though without flour during the first six weeks. The infant itself was allowed to determine the size of its meals, and in that way came to receive a larger daily quantity than is normal in infants of corresponding age. It was a robust, contented baby and its weight increased by about 1 kg per month, but it constantly had fairly severe flatulence, though without any appreciable subjective symptoms. Both flatus and faeces were foetid. Bacteriological examinations showed a lower bifidum count than in the other bottle-fed infants who were investigated; only on one occasion (240 million per gramme) did the number exceed the lower limit of the method. The number of other bacteria was continuously high.

Samples taken at the age of 8 months, when the child had been fed on a mixed diet for several months, showed that the bifidum count had risen to 2 800 million per gramme and the number of other bacteria had decreased. By that time the dyspeptic symptoms had subsided. It could not be determined whether over-eating was responsible for the digestive disorder, and had thereby given rise to unsuitable environmental conditions for *Bact. bifidum*, or whether the constantly low bifidum count and the intestinal symptoms were both manifestations of

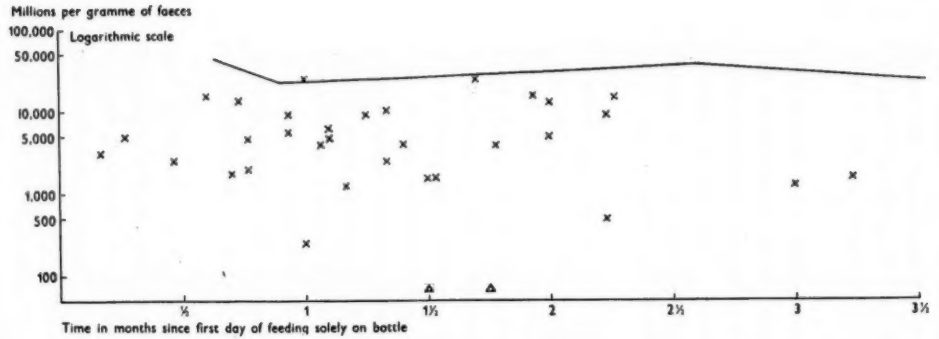


Fig. 9. Bottle-fed infants. Bifidum count in 34 infants aged from 3 weeks to 5 months, in relation to duration of feeding solely on bottle (see Table 13).

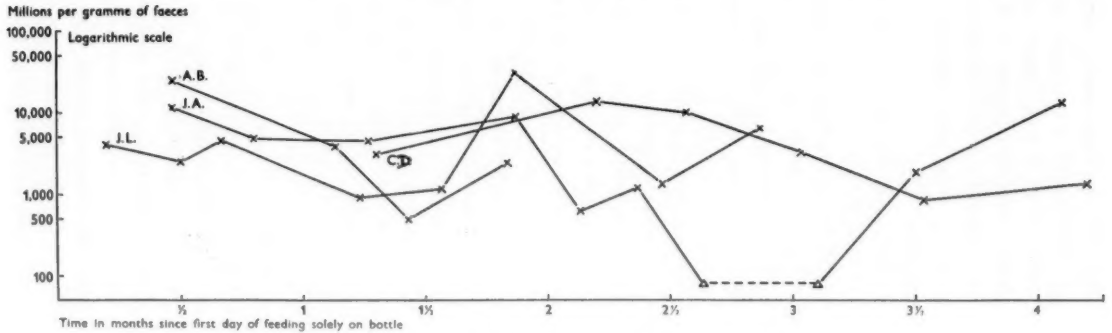


Fig. 10. Four bottle-fed infants submitted to serial tests.

Table 14

Bottle-Fed Infants Submitted to Serial Tests

Date	Faeces pH	Millions of Bacteria per 1 g of Faeces			Diet
		Coliform	Growing on Dextrose Agar	Bact. Bifidum	
	J. L. Born 21.2				
15.3	8.3	220	3 110	4 320	Half-milk formula since 10.3
24.3	7.0	210	2 280	2 500	
29.3	8.1	1 020	3 640	4 830	
15.4	8.6	7 700	9 800	945	
25.4	8.1	670	3 210	1 140	
4.5	8.2	320	4 000	31 500	
22.5	7.8	202	325	1 360	
2.6	8.2	480	1 060	6 880	
	C. D. Born 6.12				
25.1	8.9	360	1 140	2 900	Half-milk formula since 20.12
27.2	8.5	12	6 500	15 210	
14.3	8.1	81	1 400	10 500	
31.3	8.3	23	1 730	3 480	
13.4	7.6	9	200	870	
9.5	8.2	< 1	123	1 500	
	J. A. Born 20.1				
7.3	8.6	13 100	50 100	12 000	Citric acid milk since 21.2
16.3	8.1	190	18 300	4 800	
28.3	8.6	1 470	7 100	4 500	
14.4	8.4	1 830	12 800	8 400	
21.4	8.7	470	910	620	
28.4	8.5	45	820	1 250	
6.5	8.4	270	7 300	< 100	
20.5	8.1	1 400	2 530	< 100	
2.6	8.2	277	740	1 900	
20.6	8.2	190	710	14 000	

Fig. 10. Four bottle-fed infants submitted to serial tests.

(Table 14 cont.)

Date	Faeces pH	Millions of Bacteria per 1 g of Faeces			Diet
		Coliform	Growing on Dextrose Agar	Bact. Bifidum	
J. O. Born 10.3					
17.4	6.3	3 200	9 400	440	Citric acid milk since 24.3
27.4	7.0	23	2 450	4 770	
17.5	5.4	1 900	2 240	< 100	
7.6	6.5	1 240	2 400	7 700	
16.6	6.0	930	1 750	—	Half-milk formula since 16.6
26.6	7.6	880	1 310	< 100	
A. B. Born 4.12					
4.3	7.8	250	800	25 000	Citric acid milk since 18.2
23.3	7.9	430	620	6 500	
31.3	8.0	470	440	558	
13.4	8.2	32	167	2 350	
A. M. Born 24.11					
4.3	8.1	1 160	5 300	1 350	Citric acid milk since 18.2
15.3	8.2	38	3 400	1 880	
31.3	7.4	780	1 170	7 000	
13.4	8.0	1 280	1 530	4 250	
S. S. Born 4.3					
15.6	8.1	870	1 460	—	Citric acid milk since 1.6
22.6	8.2	640	710	4 400	
17.7	7.9	10	253	40	
4.8	8.0	74	390	459	
F. K. Born 1.12					
20.12	8.3	350	1 010	< 100	Citric acid milk since 6.12
18.1	8.4	6 100	8 000	2 880	
31.1	8.5	5 800	6 900	650	
T. D. Born 17.5					
1.7	7.1	2 000	4 000	< 100	Citric acid milk since 1.7
10.7	7.3	1 000	2 130	10 200	
17.7	7.1	800	2 800	3 150	

Table 15

Bottle-Fed Infant Who at No Time Received Breast Milk (L. B. Born 11.2)

Date	pH	Millions of Bacteria per 1 g of Faeces			Diet
		Coliform	Growing on Dextrose Agar	Bact. Bifidum	
20.3	8.2	820	7 200	< 100	Half-milk formula without flour
31.3	8.3	3 480	3 630	< 100	
18.4	7.9	2 250	3 680	480	Half-milk formula with flour
5.5	8.0	3 650	3 490	< 10	
26.5	—	6 500	12 100	< 10	
18.10	7.1	—	1 650	2 800	Mixed diet

a more profound bacteriological disharmony having no connection with an excessive supply of food. The bacteriological status observed when the infant had changed to a mixed diet was consistent with that found in infants of corresponding age fed on the same diet.

Summary

This investigation showed that in a series of 34 non-infected bottle-fed infants between the ages of 3 weeks and 6 months, the bifidum count varied between < 100 million and 30 000 million, the mean value being 4 000 million per gramme. Seventy-five per cent of the values were lower than 10 000 million per gramme. Other bacteria varied considerably in number, the mean value in respect of bacteria growing on dextrose agar being 1 600 million per gramme of faeces. No correlation could be demonstrated between the number of *Bact. bifidum* and that of other bacteria. In each case the pH ranged between seven and nine. In no respect was any difference found between the infants who received citric acid milk and those who received half-milk formula.

A continuous investigation of seven of these infants over a period of 1 $^1/_2$ to 4 months demonstrated conditions consistent in all respects with those reported above. No tendency was found towards any change with increasing age.

CHAPTER IV

Supplemented Breast Feeding

Earlier Investigations

The changes which occur in the faeces, especially with regard to *Bact. bifidum*, when breast feeding is supplemented by foods of various kinds, have earlier been investigated, though not extensively, by OLSEN (1949). On the basis of serial tests on a number of infants, he claims to have demonstrated that the bifidum count remains unchanged in the main, but that the pH becomes neutral or alkaline, and the odour faecal, as soon as cow's milk is added to the diet.

Personal Investigations

The aim of this section of the investigation was to elucidate in what way the bifidum count declines with decreasing volumes of suckled breast milk, and whether any significance attaches to the choice of supplementary foods relative to the maintenance of a high bifidum count.

The investigation comprised 43 clinically symptom-free infants between the ages of 1 and 8 months. All of these infants were suckled by the mothers and received supplementary food. The amount of breast milk varied between 50 and 800 g per day. The supplementary food consisted of the following.

Citric acid milk	12 infants
Half-milk formula	21 infants
Food containing no cow's milk	10 infants

Each infant received only one of these supplementary foods.

One sample was taken from each infant [though two samples (850 and 926) in group 2 were taken from the same child with an interval of one month]. The infants had a diet that was unchanged in principle for a period of one, and in most cases several, weeks before the sample was taken.

Results

The results of the faeces tests are shown in Table 16 and Fig. 11. In the former the cases are arranged in the respective groups on the basis of the bifidum count, and in the latter the bifidum count is given in relation to the daily quantity of breast milk.

The groups with different supplementary foods are fairly uniform with respect to bifidum count and pH values. The

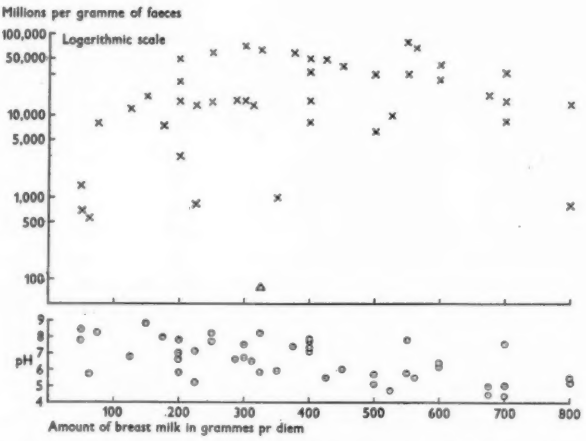


Fig. 11. Breast-fed infants with supplementary food. Bifidum count (×) and pH value (o) in the faeces of 43 infants aged from 1 to 8 months, in relation to daily amount of suckled breast milk.

number of other bacteria is lowest in the third group, which comprises, however, a relatively greater number of infants with a large quantity of breast milk. A comparison of infants with the same amount of breast milk from each of the three groups shows no significant difference either with regard to the bifidum count or with regard to the pH values.

According to Fig. 11, the infants with amounts of breast milk down to about 200 g per day had a bifidum count consistent in principle with that found in breast-fed infants (see Chapter I), whereas in those with smaller quantities the bifidum count

Table 16

Breast-Fed Infants with Supplementary Food

No. of Sample	Age	Breast Milk per Diem (g)	Faeces		Millions of Bacteria per 1 g of Faeces		
			Odour	pH	Coliform	Growing on Dextrose Agar	Bact. Bifidum
	Citric Acid Milk						
518	2 months	320	A	5.8	3 220	3 170	< 100
527	2 »	60	F	5.7	5 200	9 200	600
533	2 »	225	A	5.2	13 000	18 700	900
577	2 »	350	»	5.9	2 100	2 200	1 090
831	2½ »	50	F	8.4	2 000	19 400	1 500
319	1 »	500	A	5.1	10	10	6 500
657	3 »	525	»	4.7	325	342	10 000
506	1 »	225	F	7.1	400	1 200	13 600
318	2 »	700	A	5.0	320	700	15 000
348	1 »	400	F	7.3	1 400	2 700	36 000
314	2 »	400	A	6.3	690	850	51 000
532	1½ »	550	F	5.5	3 200	4 900	68 000
	Half-Milk Formula						
521	4 months	800	A	5.5	130	160	800
926	3 »	200	»	5.8	450	540	3 100
983	4½ »	50	F	7.8	50	308	7 470
612	2 »	400	A	6.1	28	49	8 200
1050	4½ »	80	F	8.2	3 350	6 400	8 600
850	2 »	700	A	5.0	83	940	10 850
1057	1½ »	150	F	6.8	2 400	2 200	11 600
544	7 »	300	»	6.6	720	570	14 400
580	1½ »	400	A	7.8	1 510	2 210	14 580
529	2 »	300	F	6.7	460	510	15 300
1058	5 »	150	»	8.8	4 900	5 600	17 000
1095	4½ »	200	»	7.0	7 800	8 800	28 000
656	2½ »	600	»	6.2	12	570	29 000
1036	2½ »	550	A	5.8	17	84	31 500
712	3 »	450	»	6.0	16	100	40 000
923	2 »	250	F	7.7	1 170	1 590	58 000
594	1 »	375	»	7.4	2 010	3 100	61 000
647	1 »	325	»	8.2	128	3 100	64 000

(Table 16 cont.)

No. of Sample	Age	Breast Milk per Diem (g)	Faeces		Millions of Bacteria per 1 g of Faeces		
			Odour	pH	Coliform	Growing on Dextrose Agar	Bact. Bifidum
315	4 months	400	F	7.7	1 500	1 570	68 000
631	1½ »	325	»	7.5	1 100	—	72 000
1022	3 »	550	»	7.8	75	805	79 000
	No Cow's Milk						
969	5½ months	175	F	8.0	170	353	8 000
852	5 »	700	A	4.4	< 1	22	8 600
479	3½ »	800	»	5.2	140	160	14 000
544	8 »	300	F	6.6	720	570	14 500
798	6 »	200	»	6.7	96	37	14 500
990	4½ »	675	A	4.5	28	25	19 000
714	6½ »	500	F	5.7	180	700	31 500
632	— »	700	»	7.8	950	945	34 000
747	7 »	600	A	6.4	210	—	44 000
613	6 »	400	F	5.5	550	600	50 000

Table 17

Daily Amount of Breast Milk in Relation to pH of Faeces in Infants with Supplemented Breast Feeding

Daily Amount Breast Milk	Number of Infants	pH > 6	pH ≦ 6
> 400 g	17	24 %	76 %
≦ 400 g	26	80 %	20 %

was within the limits of variation shown by the bottle-fed infants; *i.e.*, < 30 000 million per gramme faeces (see Chapter III).

It emerges, moreover, that the pH of the faeces was ≦ 6 in the majority of infants with > 400 g breast milk per day, and > 6 in most of those who had ≦ 400 g per day (Table 17).

Hence it would seem that, during weaning, the faeces of the breast-fed infant lose their degree of acidity earlier than their typical bifidum count.

Summary

An investigation of 43 breast-fed infants who received quantities of breast milk varying between 50 and 800 g per day, plus different kinds of supplementary foods, yielded the following results: (1) A bifidum count consistent in principle with that found in breast-fed infants may occur as long as the quantity of breast milk ingested exceeds approximately 200 g per day. (2) The pH of the faeces will usually be higher when the amount of breast milk decreases to less than 400 g per day. (3) The nature of the supplementary food does not appear to be of fundamental importance for the maintenance of a high number of *Bact. bifidum*.

UNIVERSITY OF MICHIGAN LIBRARIES

CHAPTER V

Feeding on Mixed Diets

Earlier Investigations

No survey illustrating the quantitative occurrence of *Bact. bifidum* in children fed on mixed diets has hitherto been published. In serial tests on eight infants, OLSEN (1949) found no significant difference between the bifidum level in breast feeding and in feeding on mixed diets. In the latter, the minimum and maximum recorded values amounted, respectively, to 100 million and about 60 000 million per gramme faeces. — In six adults, ORLA-JENSEN, OLSEN and GEILL (1945) obtained values ranging between about 100 million and 4 000 million per gramme (see page 8).

Personal Investigations

The present series consisted of 36 children between the ages of 5 months and 12 years, 18 of them being 1 year or less, and two over 6 years. All of them were clinically symptom-free. In some cases several samples were taken from the same child under unchanged experimental conditions, and here the second in the series has been included in the present review.

The results of the investigation are shown in Table 18. The bifidum count varied between < 10 million and 36 000 million per gramme faeces, and the number of other bacteria between < 1 million and 3 400 million per gramme. The pH was in the main above 6, and the odour was consistently faecal. The number both of *Bact. bifidum* and of other bacteria tended to be higher in children of 1 year or under than in those over 1 year, though a comparison of the logarithmic mean values showed that the difference did not reach statistical significance***. Bacteria growing on dextrose agar (a); *Bact. bifidum* (b).

Table 18

Children Fed on Mixed Diets

No. of Sample	Age	Faeces		Millions of Bacteria per 1 g of Faeces		
		Odour	pH	Coliform	Growing on Dextrose Agar	Bact. Bifidum
650	5 months	F	7.9	26	3 220	8 000
623	7 »	»	5.9	620	740	2 250
689	7 »	»	7.4	415	800	6 900
690	7 »	»	7.8	< 1	6	6 100
578	7 »	»	8.1	220	490	21 000
1012	7½ »	»	5.5	2 330	2 300	< 10
636	7½ »	»	7.3	165	240	10 100
597	8 »	»	7.4	170	440	1 100
640	9 »	»	7.4	920	110	5 000
456	9 »	»	6.4	350	460	18 000
849	10 »	»	7.4	7	600	400
635	10 »	»	6.7	610	760	36 000
401	11 »	»	7.5	30	40	1 400
520	1 year	»	6.9	1 260	1 180	5 900
519	1 »	»	6.4	600	1 000	8 300
387	1 »	»	6.5	210	280	16 000
641	1 »	»	6.8	160	190	22 500
587	1 »	»	8.4	240	1 100	8 400
879	13 months	»	6.0	28	50	4 000
334	15 »	»	7.5	< 1	< 1	2 700
817	18 »	»	7.4	1 700	3 200	< 100
464	2 years	»	6.0	500	1 200	800
1084	2½ »	»	6.2	1	17	< 10
604	2½ »	»	6.7	140	350	2 800
455	2½ »	»	7.2	3 400	3 400	2 900
110	4 »	»	6.7	< 1	50	< 10
1013	4½ »	»	6.8	3	3	< 10
1070	5 »	»	7.8	32	790	1 200
1090	5 »	»	6.3	10	30	100
420	5 »	»	8.1	110	150	1 100
1086	5 »	»	6.9	10	23	2 200
1020	5 »	»	7.4	—	58	6 100
1006	5½ »	»	7.7	1	2	1 800
1065	6 »	»	9.1	2	20	300
1044	9 »	»	6.8	1	2	2 500
534	12 »	»	6.3	600	650	< 100

	Infants 5—12 months	Children 13 months —12 years	Difference
	$n = 18$	$n = 18$	
(a)	$\bar{x} = 8.6 \pm 0.15$	$\bar{x} = 7.8 \pm 0.26$	0.8 ± 0.30 Significant*
(b)	$\bar{x} = 9.6 \pm 0.20$	$\bar{x} = 8.7 \pm 0.22$	0.9 ± 0.30 Significant**

Summary

This investigation showed that in a series of 36 healthy children between the ages of 5 months and 12 years, and fed on mixed diets, the bifidum count ranged between < 10 million and 36 000 million per gramme faeces. Children up to the age of 1 year appeared to have a higher bifidum count (mean value 4 000 million per gramme) than those over 1 year (mean value 500 million per gramme), the difference between the logarithmic mean values being statistically significant**. — At the same time the number of other bacteria in the entire group varied between < 1 million and 3 400 million per gramme. The pH in the main exceeded 6, and the odour was consistently faecal.

CHAPTER VI

Oral Administration of Alpha and Beta Lactose

Introduction and Earlier Investigations

In view of the major role that has been attributed to the bifidum flora in the intestines, it is natural that many investigators have sought to solve the problem of producing, under artificial feeding, a bifidum flora like that found in breast-fed infants. There has been talk of bifidum-promoting (bifidogenous) foods composed of bifidum-stimulating substances and with bifidum-inhibiting factors to a great extent neutralised. It is primarily BESSAU (1937, 1938) whose name has been associated with a bifidogenous mixture of this kind. More recently, however, KLEINSCHMIDT (1949), ADAM (1949), LEMBKE (1950) and MALYOTH (1950) too have developed mixtures which are said to possess similar properties. MAYER (1947—48) was able, moreover, to produce a bifidum milk which, during the period it is administered, maintains a preponderantly bifidum flora in the intestines.

Proof that this had succeeded was found partly at microscopic examination of stained smears from the faeces, and partly on anaerobic culturing on plates with culture media, including that of BLAUROCK. The gram-negative part of the faecal flora was quite overshadowed by a gram-positive bifidum flora. No quantitative determination of *Bact. bifidum* has been possible due to the lack of culture media suited thereto. MAYER (1949) admits that since *Bact. bifidum* does not grow quantitatively on plates, and since coliform bacteria grow much faster, it is impossible by this means to arrive at exact figures. In the present writer's opinion it cannot be judged, therefore, from the reports of the respective authors, whether the observed effect on the faecal flora was due to stimulation of bifidum by the bifidogenous food, or to the latter's inhibiting the other flora. Evaluated with an imperfect method, the result in both cases will be the same.

Chief among those agents which have consistently been ascribed major importance as bifidum-stimulating ingredients of these mixtures, are lactose and the sulphur-containing amino acid, cystine. This latter, the content of which is 70 per cent higher in breast milk than in cow's milk (ADAM, 1949), early played an important part as an ingredient of bifidum culture media. The action of cystine here appears to be markedly dependent on the environment, and, according to MAYER (1947—48), it stimulates bifidum only in Blaurock's culture medium and in peptone water containing lactose.

In the following, only lactose will be subjected to a closer study.

The part played by lactose as a carbohydrate for infants has long attracted interest. Since it is virtually the only carbohydrate contained in breast milk, it was thought that by substituting lactose ("physiological carbohydrate") for the vegetable sucrose in cow's milk mixtures, the bacterial flora in the intestines of bottle-fed infants could be made to resemble more closely that found in breast-fed infants. The practical experiments, however, did not serve to verify the theoretical speculations. Instead the infants showed an increased tendency to fermentation, and frequently a poorer increase in weight, wherefore it was soon decided to revert to sucrose. This failure was attributed to a difference between the lactose of breast milk and of cow's milk.

After SITTLER (1908) had shown that lactose possesses a bifidum-stimulating capacity *in vitro*, that substance assumed a prominent role in the discussion on *Bact. bifidum*. In the attempts to explain the difference in bifidum-stimulating properties between breast milk and cow's milk, it seemed plausible to attribute it to the different forms of lactose. According to one view, such different forms do occur here, the equilibrium between the sterical antipodes, alpha and beta lactose, being shifted toward the beta side in breast milk, and toward the alpha side in cow's milk. It is not easy to elucidate the true conditions in this respect, since polarimetrical examinations of milk are, for several reasons, very difficult to carry out. SAVELSBERG has found a ratio of 1 : 2.7 between alpha and beta lactose, both in fresh

and in boiled breast milk, and a ratio of 1 : 1.68 in cow's milk. HABILD (1949), on the other hand, was unable to observe any difference between breast milk and cow's milk with respect to the lactose equilibrium; he found the ratios to be the same as those in aqueous solution. According to investigations conducted by POLONOVSKI and LESPAGNOL (1931), breast milk contains, in addition to its common lactose (4-glucose-β-galactoside), a small amount of two isomers, allolactose (6-glucose-β-galactoside) and gynolactose. However, their findings have not yet been verified, or even subjected to further investigation.

MALYOTH (1933) propounded the theory that certain isomers of the sugars are species specific (*körpernahe*) and that their counterparts in the organism are specifically adjusted ferments; and he suggested that beta lactose is the species-specific lactose of the human organism. GERSTLEY and his co-workers (1935, 1936) found that beta lactose added to dilute cow's milk formulas brought about an increase in the gram-positive faecal flora. Later, MALYOTH and KIRIMLIDIS (1939) claimed to have shown that beta lactose *in vivo* has a bifidum-stimulating action not possessed by alpha lactose. MALYOTH (1950) reaffirmed this view on the bifidum-stimulating property of beta lactose after experimenting with a bifidogenous food of which beta lactose was an essential ingredient. This food has been clinically tested by DÜSTERWALD, KASTNER and MÜLLER (1950), too, with good results.

Other investigators have arrived at the same view concerning beta lactose. PRIMNIG and TURKUS (1943), for instance, found that on weaning healthy breast-fed infants with beta lactose for sugar in the cow's milk formula, they could obtain a preponderance of *Bact. bifidum*, which was not possible with alpha lactose or sucrose. In their opinion the bifidum-stimulating effect of beta lactose is established beyond all doubt. Further, SCHIMANSKY (1943) obtained *Bact. bifidum* more rapidly in healthy bottle-fed infants when beta lactose was used than when alpha lactose was used for sugar in the milk mixture. He considers that it has therefore been proved that bifidum can be produced with beta lactose in clinically symptom-free infants. In several of the

investigations outlined in the aforegoing, it was observed that concurrently with the administration of beta lactose the pH of the faeces fell to 5—6 and the odour became acid.

BESSAU (1943), MÜLLER and ROMINGER (1948) and others consider, on the other hand, that no substantial difference can exist between the effects of alpha and beta lactose in the intestine. They call attention to the rapid shift toward a state of equilibrium which both forms of lactose undergo in aqueous solution. KLEINSCHMIDT (1949), on experimental administration of alpha and beta lactose to infants, found in both instances a preponderating bifidum flora in faecal smears.

OLSEN (1949), using his quantitative method, determined the number of *Bact. bifidum* in some healthy bottle-fed infants and some that were dyspeptic, while their cow's milk diets were modified in different ways, including the substitution of alpha lactose for the usual sucrose. In several of the experiments on infants in the first-named category the bifidum count increased during the lactose period. No changes were observed in the physical characteristics of the faeces. With regard to the dyspeptic infants, OLSEN sums up as follows: "There does seem to be an indication that lactose, and in part glycose, in amounts of 5—7 per cent of the diet has a stabilizing action on the flora, which does not seem to be the case with sucrose."

In view of the methods used in earlier investigations *in vivo*, the results obtained there do not permit any definite conclusions on the influence of alpha and beta lactose, administered by mouth, on the bifidum flora in the intestines.

Personal Investigations

The practical problem which this part of the investigation is mainly designed to elucidate, might be expressed as follows: Can oral administration of beta lactose, in contrast to alpha lactose, produce a quantitatively demonstrable increase in the number of *Bact. bifidum* in the faeces of healthy children who are not fed on breast milk?

Lactose (milk sugar) is a disaccharide which in the animal organism occurs only in the milk. It is composed of the monosaccharides

glucose and galactose, into which constituents it is separated by the intestinal ferment, lactase. Lactose constitutes the principal carbohydrate of milk and is formed by some process in the mammary glands that still remains to be elucidated.

Lactose occurs in several modifications, of which alpha and beta lactose are of some interest in this context. Alpha lactose (α-glucose-β-galactoside) crystallizes from aqueous solution at temperatures below 93.5°, with one mol water of crystallization (the commercial form of lactose). Its mutarotation formula is

$$(\alpha)\ \frac{20}{D} = +\ 83.5 \rightarrow +\ 52.3.$$

Beta lactose (β-glucose-β-galactoside) crystallizes from aqueous solution at temperatures over 93.5°, without water of crystallization, and has the formula

$$(\alpha)\ \frac{25}{D} = +\ 34.2 \rightarrow +\ 52.3.$$

Beta lactose is more soluble in water than alpha lactose, and has a sweeter flavour. In an aqueous solution of both forms, the one shifts toward the side of the other, so that a stable equilibrium arises in due course. This change can be studied polarimetrically and proceeds relatively rapidly at the outset. In a 5 per cent solution at 21—22° C, alpha lactose virtually attains the final rotation of 53° after five hours, whereas beta lactose under corresponding conditions attains 50.2° in 3 $^1/_2$ hours. (Malyoth and Kirimlidis)

The beta lactose used in the following experiments was prepared by *AB Svenska Mjölkprodukter* and had a degree of purity of 96—98 per cent. The alpha lactose used here was the commercial *Saccharum lactis*.

Case Material

The experimentees were referable to three age groups; namely:

Group 1. Four infants who were 2—3 weeks old at the start of the experiments, prior to which their diet had been changed in about 3 days from heated breast milk to citric acid milk.

Group 2. Four infants who were 1 $^1/_2$—4 months old at the start of the experiments and who had been fed for at least three weeks on citric acid milk or half-milk formula.

Group 3. Eleven infants and children between the ages of 7 months and 2 $^1/_2$ years, who were fed on mixed diets. None of the children had received breast milk during the month immediately preceding the experiments.

Most of these experimentees were nursed at children's homes, but a few at the Sachs Hospital for Children or in their own homes. All of them were clinically symptom free. If any child developed an upper respiratory tract infection, the experiment was discontinued and not resumed for at least one week after the symptoms had subsided.

The experimental procedure was as follows. The children received alpha and beta lactose for periods of 6—20 days, usually about 15 days. Five were given beta lactose only. In groups 1 and 2 the sucrose in the cow's milk formula was replaced by alpha or beta lactose; in group 1 in the same proportion (7 per cent), and in group 2 with 15 per cent (in infant D. I., 7 per cent) of the amount of food. The lactose was added to the heated mixture immediately before feeding. In group 3, on the other hand, alpha and beta lactose were given, in addition to the ordinary diet, in a daily dose of 3.5 g per kilogramme body weight per day, divided into three portions. The lactose was dissolved in a suitable quantity of water immediately before feeding, and was given in conjunction therewith.

Samples of the faeces were taken before, during and after each period of feeding, and intervals of about 14 days elapsed between the periods.

Results

The investigatory results are summarized in Tables 29 to 31 and Figs. 12 to 29. (Table 32 and Figs. 30—31 include two untreated normal cases.) Explanatory notes see page 83.

As will be seen from the diagrams, the bifidum curves show no uniform effect of the administration either of alpha or of beta lactose. Some of the infants (K. B., B. O. and P. N.) show a distinct and even rise during the beta lactose period, but no corresponding rise during the alpha lactose period. In the case of infants A. O. and K. E., the converse is true. Otherwise the

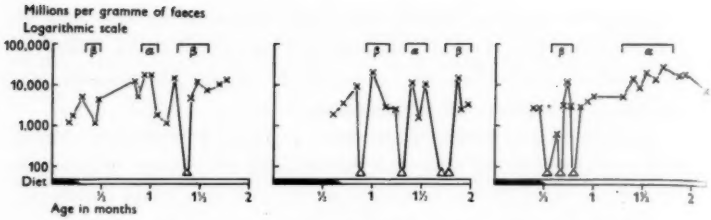


Fig. 12.
L. B. Born March 26.

Fig. 13.
B. L. Born Apr. 6.

Fig. 14.
A. O. Born Jan. 1.

Figs. 12—14. Bifidum count on administration of alpha and beta lactose. Group 1. Three infants who were 2—3 weeks old at the start of the experiments, prior to which their diet had been changed in about 3 days from heated breast milk to citric acid milk (see Table 29).

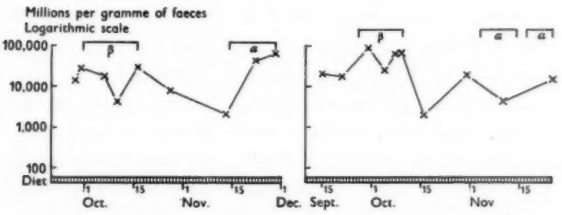


Fig. 15.
K. L. Born June 9.

Fig. 16.
P. N. Born May 9.

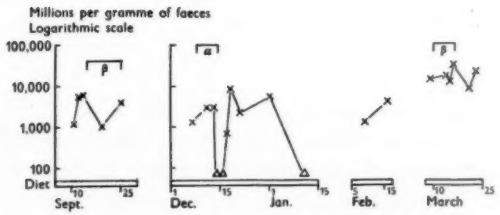


Fig. 17.
K. Å. Born Aug. 2.

Fig. 18.
D. I. Born Oct. 27.

Figs. 15—18. Bifidum count on administration of alpha and beta lactose. Group 2. Four infants who were 1 $^1/_2$—4 months old at the start of the experiments and who had been fed for at least 3 weeks on citric acid milk or half-milk formula (see Table 30).

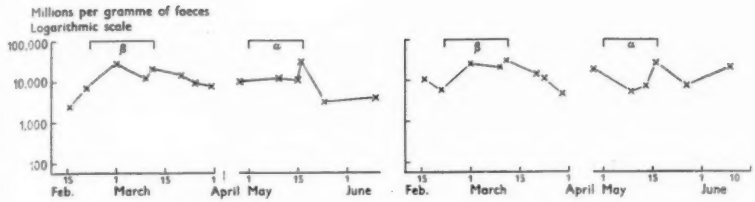


Fig. 19.
Y. E. 7 months.

Fig. 20.
K. B. 8 months.

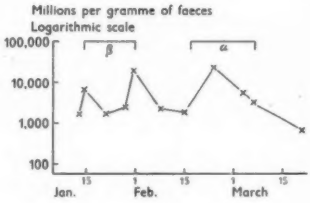


Fig. 21.
K. A. 13 months.

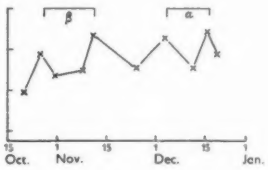


Fig. 22.
U. J. 11 months.

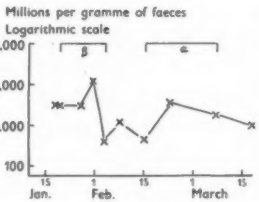


Fig. 23.
P. W. 2½ years.

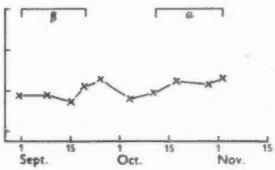


Fig. 24.
M. B. 2 years.

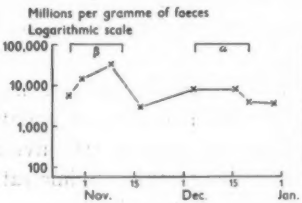


Fig. 25.
B. O. 11 months.

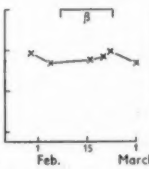


Fig. 26.
L. T. 9 months.

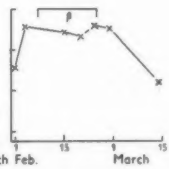


Fig. 27.
B. A. 10 months.

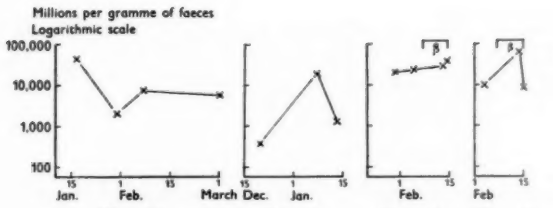


Fig. 30. F. H. 6 months. Fig. 31. B. L. 6 months. Fig. 28. A. K. 1 year. Fig. 29. A. S. 7 months.

Figs. 19—29. Bifidum count on administration of alpha and beta lactose. Group 3. Eleven children aged from 7 months to 2 $^1/_2$ years, who were fed on mixed diets. None of them had received breast milk during the month immediately preceding the experiments (see Table 31).
Figs. 30—31. Bifidum count in two infants fed on mixed diets with no supplementary lactose (see Table 32).

curves exhibit temporary peaks, which occurred both during the alpha lactose and during the beta lactose period, and occasionally before.

The variations in group 1 are probably not connected with the administration of lactose, but point to an instability in the bifidum count in infants weaned rapidly and at a very early stage; for such an instability was observed under these conditions in three cases without lactose (see Tables 19 and 30).

To clarify the conditions associated with administration of the respective forms of lactose, the following computation was made. In the infants comprising groups 2 and 3 (excluding infant D. I.) the common logarithmic mean of two bifidum values (in three infants one value) before the respective lactose periods was compared with the corresponding mean during those periods. In one case the last two values were taken; in the other case the first and the last.

The results suggest that both alpha and beta lactose under the relevant experimental conditions had a certain stimulating effect on the bifidum flora. The bifidum count on the average was 100 per cent higher during than before the administration of either type of lactose. The difference is not significant, possibly because of the small number of cases.

Table 19

Infants Changed from Heated Breast Milk to Bottle Feeding for a Few Days in the First Two Weeks of Life

Date	Faeces pH	Millions of Bacteria per 1 g of Faeces			Diet
		Coliform	Growing on Dextrose Agar	Bact. Bifidum	
B. F. Born 4.11					
11.11	5.3	1 290	1 310	2 100	Heated breast milk
12.11	5.7	8 700	9 500	2 180	» » »
15.11	8.2	11 800	12 200	< 100	Citric acid milk since 15.11
18.11	7.8	2 360	2 550	170	
22.11	6.5	4 120	4 820	< 100	
25.11	8.2	4 500	8 200	< 100	
F. L. Born 13.8					
22.8	5.2	< 1	< 1	370	Heated breast milk
23.8	5.3	20	30	4 300	» » »
24.8	5.3	< 1	< 1	2 500	» » »
25.8	5.5	< 1	< 1	1 300	» » » 50 %
27.8	6.5	7 400	12 200	2 100	Citric acid milk since 27.8
G. K. Born 8.11					
19.11	5.7	2 380	2 380	9 000	Heated breast milk
20.11	5.0	2 170	2 290	4 000	» » »
24.11	5.2	1 290	1 300	600	Citric acid milk since 24.11
29.11	8.2	1 600	2 270	320	
3.12	7.9	7 300	7 300	600	
10.12	6.6	1 530	1 750	< 100	
17.12	8.2	2 700	3 200	1 080	
20.12	8.8	1 400	1 440	—	
31.12	9.0	4 400	5 400	—	

Nor was the number of other bacteria unequivocally influenced by the administration of either form of lactose. The same applied to the pH and the physical characteristics of the faeces. The infants in Group 1, who showed variations in this respect, were exceptions. The mother of infant P. N. stated that

Table 20

Bifidum Count (Logarithmic Mean) in Children without Breast Milk, between 1 Month and 2½ Years, before and during Administration of Alpha and Beta Lactose. Each Child Represented by Two Values before and Two during Lactose Period*

	Administration of					
	Alpha Lactose			Beta Lactose		
	Before	During	Diff.	Before	During	Diff.
Group A (9 children) ...	9.55	9.90	0.35	9.66	10.0	0.34
Group B (5 children) ...	—	—	—	9.81	10.20	0.39
A + B (14 children)				9.71	10.10	0.39

Group A. Nine children tested with both alpha and beta lactose.
Group B. Five children tested with beta lactose alone.

the stools were looser than usual during the first week of each lactose period.

Discussion

The results described above show that both alpha and beta lactose, on oral administration to children in the first years of life, may produce an increase in the bifidum count. In the present series, this increase varied considerably, and in several cases was quite absent. On the average it approximated to a doubling of the bifidum count, with respect to both types of lactose.

As regards beta lactose, the present investigation is the first attempt that has hitherto been made to elucidate with a quantitative method any effect which it may have on the bifidum flora in the intestine. In this connection no evidence emerged to support the assumption that beta lactose may have a specific bifidum-stimulating action which alpha lactose does not possess. This accords with what we might expect to find *a priori*, having regard to the instability of the lactose isomers in water solution. It does not necessarily follow, however, that the relevant condi-

* In three infants one value before lactose period.

tions in a neutral water solution will be identical with those which are subject to the specific conditions of acidity in stomach and intestine.

Due to differences in method, these results do not lend themselves to a comparison with those of previous investigators, other than OLSEN (1949). However, the last-named only investigated alpha lactose. His results too showed that alpha lactose administered to healthy infants may produce, in certain cases, a moderate increase in the bifidum count without any changes in the physical characteristics of the faeces or any demonstrable reaction in the other intestinal flora. In Olsen's experiments alpha lactose was substituted for the usual sucrose.

Several of those investigators who are convinced of the bifidum-stimulating role of lactose (alpha or beta), as an ingredient of artificial foods for infants, state that the best effect is found in dilute cow's milk formulas (BESSAU, 1938; SCHIMANSKY, 1943; KLEINSCHMIDT, 1949; and others). GERSTLEY and his co-workers (1935) considered that certain factors in cow's milk promote the development of a gram-negative bacterial flora in the bowel, and that these factors are proportional to the amount of cow's milk in the diet. A mixture of cow's milk containing beta lactose will produce a more abundant gram-positive flora when diluted with water than when undiluted. Other investigators have found, however, that whole milk, and even acidified whole milk, can be used to advantage (ADAM, 1949).

In the present investigation, the age of the experimentees varied from 1 month to $2\,^1/_2$ years. The diets included citric acid milk, half-milk formula, and mixed diets. No evidence was found that any of these factors might promote the bifidum-stimulating capacity of lactose, if such it possesses.

In feeding infants on foods containing beta lactose, several authors (see page 64), using quantitative methods, have observed a conspicuous shift in the intestinal flora toward the side of a gram-positive bifidum flora. Judging by the results presented here, it seems improbable that the main cause of this change is to be sought in a bifidum-stimulating effect of lactose, and in particular beta lactose. KRISTEN and PETUELY's (1950) dis-

covery that their so-called bifidum-stimulating substance did not affect the bifidum bacteria, but rather inhibited the other flora, suggests that the action of the bifidogenous mixtures may be of somewhat similar nature. Nevertheless, it is evident that a certain bifidum-stimulating effect of lactose cannot be ruled out. If the other bacterial flora in the faeces is inhibited, *Bact. bifidum* may be found to preponderate on microscopic examination of stools, provided the findings are not checked by quantitative determinations.

Summary

To establish whether the bifidum flora in the bowel may be influenced by oral administration of lactose, primarily beta lactose, the following investigation was conducted. A number of healthy children between the ages of 2 weeks and 2 $^1/_2$ years were given alpha and beta lactose for separate periods of about 15 days (6—20 days). During these periods regular tests were made of the stools, with respect to physical characteristics, pH and bifidum count. In addition the number of bacteria growing on endoagar and dextrose agar was determined. The lactose was either substituted, in the same or double the amount, for the usual sucrose in the cow's milk formula, or supplemented the ordinary diet in doses of 3.5 g per kilogramme body weight per day. In each case the lactose was dissolved in a liquid immediately before the meal.

The investigation tends to show that both alpha and beta lactose, administered by mouth, may produce in certain cases a moderate increase of the bifidum count in the faeces. The increase is not significant. No difference was found between alpha and beta lactose with respect to bifidum-stimulating capacity. Nor did any unequivocal changes occur in certain other faecal flora or in the physical characteristics of the stools during the period in which lactose was administered.

CHAPTER VII

Tests of the Susceptibility of Bacterium Bifidum to Antibiotics and Sulphonamide

Earlier Investigations

Few investigations have been made hitherto into the effect of antibiotics and chemotherapeutical agents on *Bact. bifidum*. BESSAU (1943) stated that the growth of *Bact. bifidum* in the bowel could be totally arrested or inhibited by arsenic-containing drugs such as Spirozid. ADAM (1949) reported that in experiments *in vitro*, *Bact. bifidum* was found resistant to streptomycin (even in a 3 per cent concentration in a fluid medium), but that penicillin and sulphonamide in therapeutic doses inhibited its growth.

MALYOTH (1950) found that penicillin and sulphonamide distinctly reduced the percentage of *Bact. bifidum* in the bacterial flora in gram-stained smears; indeed, occasionally the bifidum bacteria disappeared altogether. However, the observations (MALYOTH and SPANIER, 1950) in many cases seem to have been made during the course of an infection, so that the cause of the effect must be considered very difficult to judge.

No reports have earlier been published on the susceptibility of *Bact. bifidum* to aureomycin and chloromycetin.

Personal Investigations

These comprised tests of the susceptibility of *Bact. bifidum*, *in vivo* mainly to aureomycin, chloromycetin and penicillin, and *in vitro* to penicillin, streptomycin and sulphonamide (Elkosin).

Case Material

The tests *in vivo* were carried out on infants between the ages of 2 and 4 months, together with one 9-year-old girl, all of them being nursed at the Sachs Hospital for Children. The

infants had been fed since birth solely on heated breast milk. Most of the tests were made on the infants earlier dealt with in Chapter II. In these cases the experiments did not start as a rule until the bifidum count had attained the relatively constant higher level mentioned in that chapter. Most of the penicillin tests were made, however, on other, somewhat younger infants, in whom a rise in the bifidum count could still be expected. To this circumstance should probably be attributed the rise in the bifidum count that occurred in two cases during the course of penicillin treatment (infants E. N. and M. M.).

Two of the experimentees (Y. E. and K. B.) developed nosocomial infection of the upper respiratory tract in an interval between two tests, but otherwise the infants presented no signs of intercurrent diseases. The 9-year-old girl was suffering from acute toxoplasmosis but presented no clinical symptoms in the bowel.

In the resistance tests *in vitro*, 10 to 11 determinations were made on strains from nine children, some of whom were identical with the above-mentioned experimentees.

Method

Tests in Vivo. — Aureomycin and chloromycetin were administered by mouth to six experimentees in separate periods, and aureomycin alone to a further three. The dose was 50 mg four times daily for six days (in two cases, 10 and 12 days respectively), which in most cases corresponded to about 40 mg per kilogramme body weight per day (approximately 55 mg in respect of infants M. R. and S. H.). In some cases vitamin B was given in conjunction with aureomycin.

Penicillin was administered by mouth to four children, intramuscularly to one child, and by both routes in a further two children. Crystalline penicillin was used, the dose being about 25 000 units per kilogramme body weight per day. In oral administration this daily amount was given in five separate doses, each one-half to one hour before meals. In intramuscular administration it was given in four separate doses. In one case (E. N.), however, the procedure was different in one of the ex-

periments, penicillin procaine being administered in the form of single daily injections of 10 000 units per kilogramme body weight.

Streptomycin was administered by mouth to two children in a dose of 50 mg 4—5 times daily, corresponding to 50—60 mg per kilogramme body weight per day. The duration of treatment was eight days.

The effect of sulphonamide was not tested *in vivo*.

Tests in Vitro. — In determining the resistance, the following procedure was adopted. A number of bifidum colonies, obtained by culturing samples of faeces mainly from breast-fed infants in the manner described earlier, were removed and suspended in sterile physiological saline solution (approximately one colony per 1 ml). A certain amount of this bacterial emulsion, together with solutions, respectively, of penicillin, streptomycin and Elkosin in varying concentrations, was added to a series of small tomato agar tubes at 45—50° C. Two control tubes were used, to which only bacterial emulsion had been added. The tubes were then incubated at 37° C for three days. The growth in the respective tubes was evaluated on the basis of the control tubes. (Due to practical difficulties, no tests were made with aureomycin and chloromycetin.)

Results

The results of the tests *in vivo* are shown in Figs. 32—38 and Tables 27 and 28.

Under treatment with aureomycin and chloromycetin, the bifidum count in the stools fell so markedly that in most cases the values could not be determined with the method employed. Expressed in figures the number decreased by 90 per cent and more, ranging between one-tenth and less than one-hundredth of the original values. Under the experimental conditions obtaining here, there was no complete inhibition of the bifidum flora in the bowel. In infants G. F. and S. H., a bifidum count approximating to the values before and after treatment occurred temporarily during the course of treatment. On conclusion of six days' treatment the bifidum count in each case rose speedily

to the original levels. After 13 days' aureomycin treatment (infant E. N.) there was an interval of 7—12 days, however, before the bifidum count attained the original values. No demonstrable difference was observed between aureomycin and chloromycetin with respect to bifidum-inhibiting effect.

As regards the effect on the other bacterial flora, *B. proteus* was found to be present, but disappeared when the treatment was discontinued. The number of coliform bacteria and proteus bacilli distinctly increased in three cases of six under chloromycetin treatment. Under treatment both with aureomycin and with chloromycetin there occurred in six cases of seven an increase in the number of bacteria growing on dextrose agar, being very pronounced in certain of them. In infant M. R., monilia fungi grew in the bifidum culture medium under aureomycin treatment.

With regard to penicillin treatment, falls ranging from 30 to over 99 per cent occurred in the bifidum count after 3—16 days. The effect of a certain daily dose appeared to be stronger with oral than with intramuscular administration. This was evident, for example, in the case of infant P. Ö., who received both modes

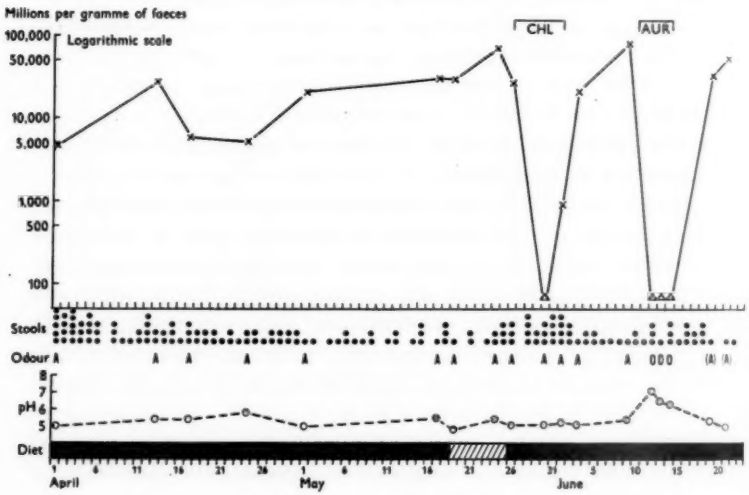


Fig. 32. M. O. Born March 11.

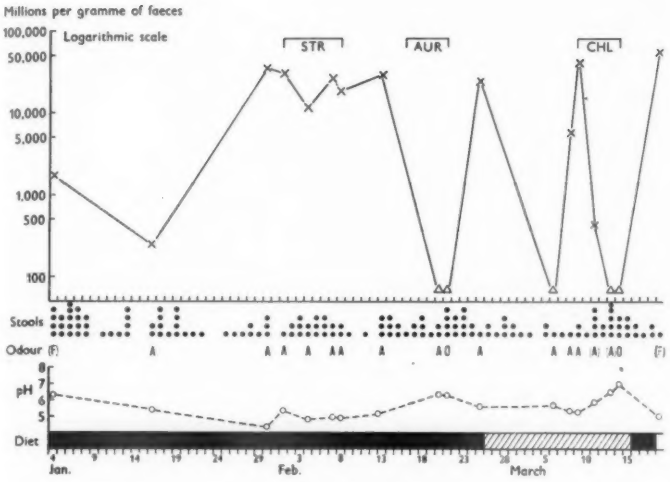


Fig. 33. Á. Z. Born Dec. 12.

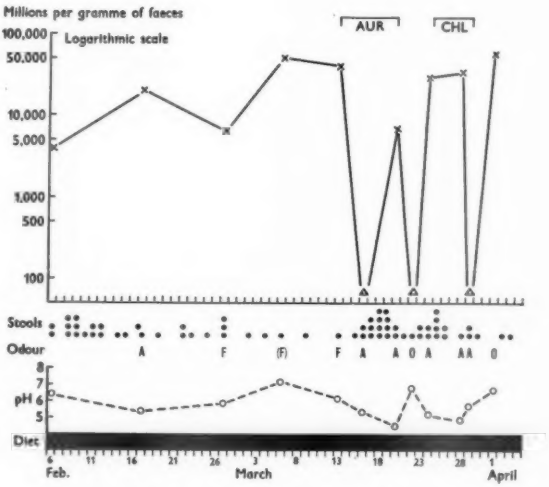


Fig. 34. T. F. Born Jan. 1.

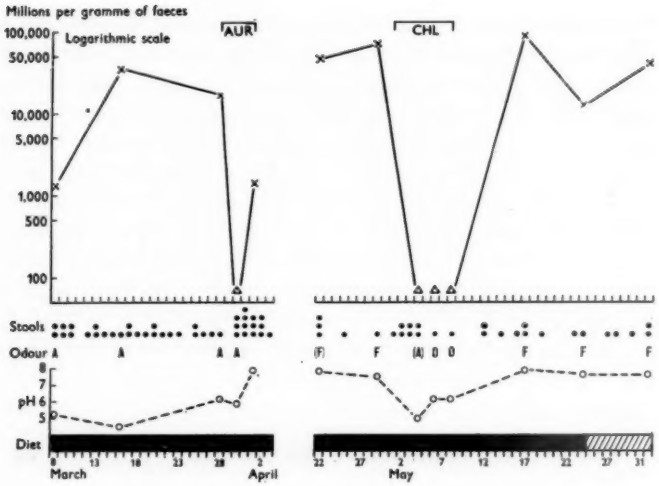


Fig. 35. Å. S. Born Jan. 11.

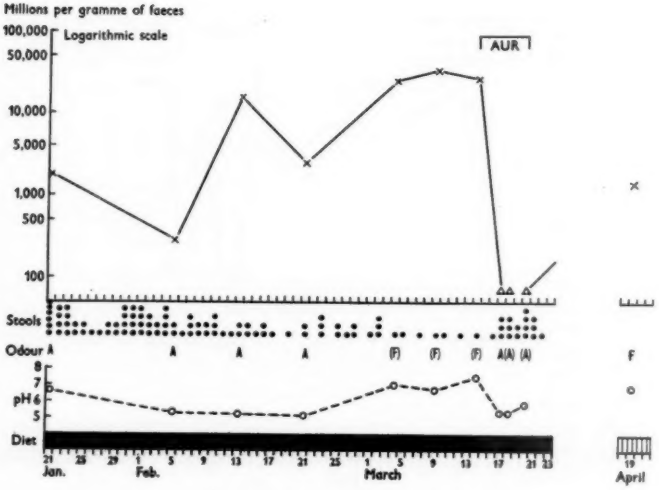


Fig. 36. K. N. Born Jan. 20.

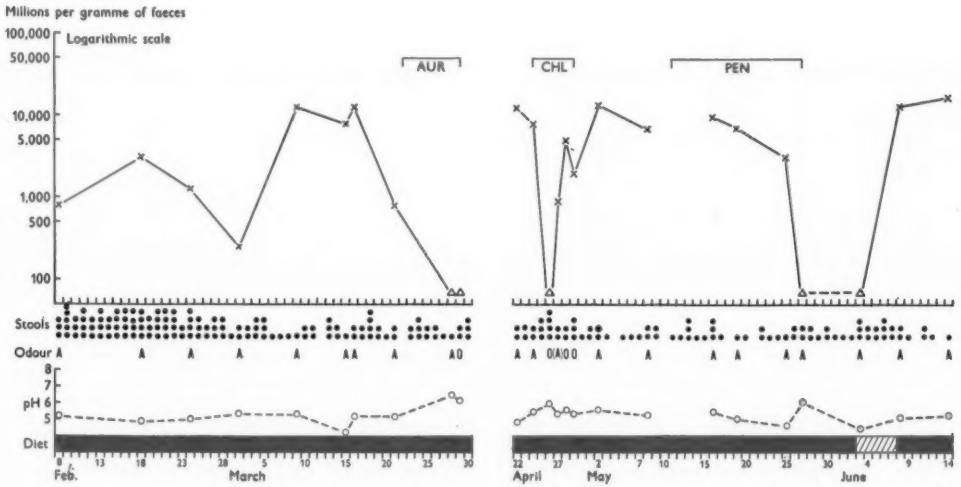


Fig. 37. M. H. Born Jan. 20.

UNIVERSITY OF MICHIGAN LIBRARIES

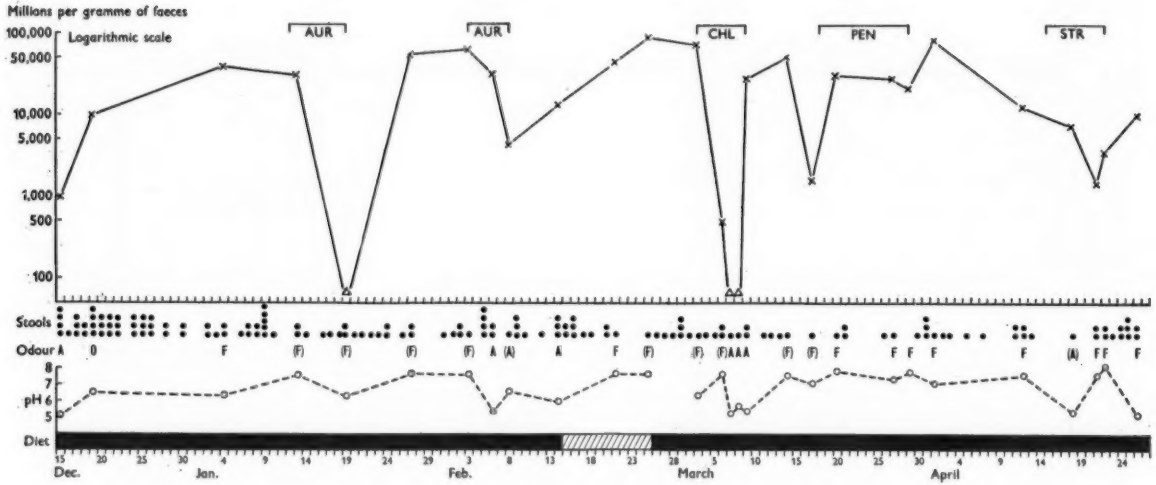


Fig. 38. S. H. Born Nov. 20.

of treatment in different periods. The bifidum count fell by over 99 per cent under oral administration and by 30 per cent under intramuscular administration. The experimental results in case E. N. show, however, that this reaction may not be the rule. Compared with aureomycin or chloromycetin treatment by mouth, oral administration of penicillin had, on the average, a slower and less conspicuous effect. — In these experiments penicillin had no demonstrable effect on the pH and the number of other bacteria.

In the one case, streptomycin in a dose of 50 mg per kilogramme body weight per day produced in the bifidum count a moderate fall of about 75 per cent to roughly one-fourth of the original values; in the other case it produced no effect in a dose of 60 mg per kilogramme body weight per day.

The results of the resistance tests *in vitro* are shown in Tables 21 to 23.

Bact. bifidum was completely inhibited *in vitro* by

Penicillin in a concentration of 1 unit but not of 0.25 units per 1 ml.
Streptomycin in a concentration of 50 mg but not of 10 mg per 1 ml.
Sulphonamide (Elkosin) in a concentration of 3.3 mg but not of 1.32 mg per 1 ml.

Figs. 32—38. Full-term infants fed on heated breast milk, submitted to serial tests and treated with antibiotics by mouth and intramuscularly (see Table 27).

Explanatory notes to Figs. 12—18, 32—38 and Table 27. The experimentees had been fed on heated breast milk since birth and none was older than four months during the experimental period. The doses per kilogramme body weight per day, and the mode of administration, were as follows: Aureomycin and chloromycetin approximately 40 mg by mouth; penicillin (crystalline) 25 000 units by mouth and intramuscularly; penicillin procaine 10 000 units intramuscularly; and streptomycin approximately 50 mg by mouth. Some of the experimentees were given, for a short time, non-heated breast milk obtained from other mothers. When fed to the infants, this milk was mostly 8—12 hours old in respect of cases M. O., M. S. and M. H., and about 24 hours in respect of cases Å. S. and S. H.

× – × – × = bifidum curve; △ = bifidum counts below 100 million per 1 g (i.e. under lower limit of method); o – o – o = pH curve; AUR = aureomycin; CHL = chloromycetin; PEN = penicillin; STR = streptomycin; ● = stool; A = acid; (A) = slightly acid; F = faecal; (F) = slightly faecal; O = indifferent odour. ■ = heated breast milk; ///// = non-heated breast milk; ▥ = half-milk formula; ▭ = citric acid milk.

Table 21

Effect of Penicillin on Growth of Bifidum Bacteria in Vitro (0 = no growth; + + + = growth equal to that in the controls)

Child	Penicillin Units per 1 ml Medium					
	1.0	0.25	0.1	0.025	0.01	0.0025
M. R.	0	0	+	—	+ + +	+ + +
E. N.: I	0	0	+	+	+ +	+ + +
P. N.	0	+	+ +	+ + +	+ + +	+ + +
K. E.: I	0	+	+ +	+ +	+ + +	+ + +
M. M.	0	0	+	+ +	+ + +	+ + +
G. L.	0	0	+	+ + +	+ + +	+ + +
P. Ö.	0	0	+	+	+ +	+ +
K. E.: II ...	0	0	+	+ +	+ + +	+ + +
G. N.	0	0	+	+ + +	+ + +	+ + +
E. N.: II....	0	+	+ +	+ +	+ +	+ + +

Table 22

Effect of Streptomycin on Growth of Bifidum Bacteria in Vitro (0 = no growth; + + + = growth equal to that in the controls)

Child	Streptomycin mg per 1 ml Medium						
	1 000	100	50	10	2.5	1.0	0.25
R. Ö.	—	—	—	+	+ +	+ +	+ + +
M. R.	0	+	—	+ +	+ +	+ +	+ + +
P. N.	0	0	0	+ +	+ + +	+ + +	—
K. E.: I	0	0	0	+	+ +	+ + +	—
M. M.	0	0	0	0	+	+ + +	—
G. L.	—	0	0	0	0	+ +	+ + +
P. Ö.	—	0	0	0	+	+ +	+ + +
K. E.: II ...	—	0	0	0	+ +	+ +	+ + +
G. N.	—	0	0	0	+ +	+ + +	+ + +
E. N.: II ...	—	0	0	0	+ +	+ +	+ + +

Table 23

Effect of Sulphonamide (Elkosin) on Growth of Bifidum Bacteria in Vitro (0 = no growth; + + + = growth equal to that in the controls)

Child	Elkosin mg per 1 ml Medium					
	0.66	3.3	1.32	0.66	0.33	0.13
R. Ö.	0	—	+	++	+++	+++
M. R.	0	—	+++	+++	+++	+++
E. N.: I	0	0	0	++	+++	+++
P. N.	0	0	+	++	+++	+++
K. E.: I	0	0	+	+++	+++	+++
M. M.	0	0	+	++	+++	+++
G. L.	0	0	0	++	+++	+++
P. Ö.	0	0	0	0	+	+++
K. E.: II ...	0	0	++	++	+++	+++
G. N.	0	0	+	++	+++	+++
E. N.: II ...	0	0	0	+	+++	+++

Clinical Observations

The general condition of the children was not affected by treatment either with aureomycin or with chloromycetin. The same was true with regard to the increase in weight, which was satisfactory in all cases. No vomiting occurred which could be attributed to the treatment. However, an impairment of the appetite was observed, being moderate in the infants but pronounced in the 9-year-old girl. In one of the infants who did not receive vitamin B during treatment with aureomycin, an intertrigo developed on the buttocks and did not heal for several weeks despite adequate treatment. An infant of one month had recurrent attacks of ileus, but they responded to simple measures. The attacks did not cease until some time after aureomycin treatment had been discontinued.

Under treatment with aureomycin and chloromycetin the stools in each case were of loose consistency and the average number of defaecations was doubled (see Figs. 32 to 38). The stools became quite homogeneous, porous, somewhat ropy, and

often welled out of the anus. They were yellow in colour. The odour, which prior to treatment had been acid in some cases and faecal in others, shifted towards an indifferent intermediate level. Corresponding changes were noted in the pH levels. In general a low pH rose and a high one fell concurrently with the treatment, at the conclusion of which both odour and pH rapidly returned to the original values. With a few exceptions, an acid odour was accompanied by a low pH, and a faecal odour by a pH around or over seven. As regards the frequency of defaecation, normal conditions were restored within a week after the conclusion of treatment.

With regard to the experiments with penicillin and streptomycin, no clinically demonstrable side-effects were observed. However, in infant M. H. a decrease in the bifidum count coincided with looser but not more frequent stools (defaecation approximately once every other day).

Summary and Discussion

The susceptibility of *Bact. bifidum* to certain antibiotics and to sulphonamide (Elkosin) was tested partly *in vivo*, mainly with oral administration, and partly *in vitro*. The experimentees with a few exceptions consisted of full-term infants aged from 2 to 4 months and fed from birth on heated breast milk.

Aureomycin and chloromycetin, in doses of approximately 40 mg per kilogramme body weight per day, were found to have a pronounced inhibitory effect on the growth of *Bact. bifidum* in the intestines. The bifidum count decreased under treatment by 90 per cent or more, in most tests to less than one-hundredth of the original value. In the majority of cases the number of bacteria growing on dextrose agar showed, concurrently, a conspicuous rise. *Bacillus proteus* coexisted with the coliform bacteria. The effect on the bacterial flora persisted as long as treatment proceeded, after which there was a spontaneous return to normal conditions.

The duration of treatment with aureomycin and chloromycetin was limited to six days so as to lessen the risk of untoward side-effects, mainly a preponderance of pathogenic intestinal flora.

Only in two cases was aureomycin given, in conjunction with vitamin B, over a longer period (10 and 13 days respectively). Hence the durations of treatment were too short to permit of any far-reaching conclusions. The general tendency none the less is quite evident. It is clear too that the longer treatment proceeds, the more difficult it will be for *Bact. bifidum* subsequently to attain normal values.

Penicillin, in a dose of 25 000 units per kilogramme body weight per day, was also found to inhibit the growth of bifidum *in vivo*, although the effect in several cases was more gradual and less conspicuous than that of aureomycin and chloromycetin. The investigation tends to show that a certain daily dose of penicillin will have a stronger effect on the bifidum flora when administered by mouth than when administered intramuscularly. From the standpoint of bifidum growth the latter mode of administration is therefore the method of choice, particularly as the therapeutic dose by mouth must be higher.

In the tests with penicillin *in vitro*, the growth of bifidum was found to be completely inhibited in a concentration of 1 unit but not in a concentration of 0.25 units per millilitre.

Streptomycin *in vivo* produced a fall of 75 per cent in the bifidum count in one case, but no effect at all in the other case. Tested *in vitro*, streptomycin completely inhibited the growth of *Bact. bifidum* in a concentration of 50 mg but not in a concentration of 10 mg per millilitre.

Sulphonamide (Elkosin) was tested only *in vitro*. It produced complete inhibition of *Bact. bifidum* in a concentration of 3.3 mg but not in a concentration of 1.32 mg per millilitre.

Clinical side-effects were observed only under treatment with aureomycin and with chloromycetin. The impairment of appetite that occurred in the infants was of a considerably milder degree than that found in older children. In the former the stools consistently became looser, more homogeneous and more frequent, the odour concurrently becoming less acid or indifferent. An infant of one month had recurrent attacks of ileus, but they could be arrested by simple measures. Since the infants were fully healthy, the symptoms must undoubtedly be attributed to the

drugs in question. In treatment with these antibiotics, such symptoms should therefore be borne in mind, so as to preclude their being erroneously interpreted as signs of intestinal infection.

All antibiotics currently in use have a wide therapeutic range. Consequently they affect, among other things, the physiological intestinal flora. The bacterial equilibrium becomes disrupted and pathogenic organisms such as *B. proteus*, *B. pyocyaneus* and monilia fungi may gain the ascendancy and give rise to complications, sometimes with a fatal outcome.

It is therefore important to elucidate the reaction of the bifidum flora to these antibiotics and chemotherapeutical agents.

Tabulation of Results Described in Chapters I, II, III and V

The results obtained in the principal diet groups are surveyed in Tables 24—26. Each group consists of different experimentees, and each of the latter is represented by only one value in the relevant table.

General Summary and Discussion

In the series presented here the bifidum count in breast-fed infants ranged between approximately 1 000 million and 150 000 million per gramme faeces, whereas in the children who were not breast fed it did not exceed approximately 35 000 million per gramme. The differences between the logarithmic mean value of the group comprising breast-fed infants and the logarithmic mean values of each of the other four groups are significant ***, these differences being

(1) 1.0 ± 0.092 (infants mainly under one month fed on heated breast milk)

(2) 0.9 ± 0.13 (bottle-fed infants)

(3) 0.9 ± 0.21 (infants fed on mixed diets)

(4) 1.8 ± 0.23 (children over one year fed on mixed diets).

A comparison between the four last-named groups shows that the bifidum counts in the three infant groups (1, 2 and 3) are of the same magnitude. In relation to these the bifidum count is lower in children over one year. The differences between the logarithmic mean values of group 1 and 2 respectively and group 4 are significant ***, the differences being 0.8 ± 0.23 and 0.9 ± 0.25 respectively. The corresponding difference between group 3 and 4 is significant **, the difference being 0.9 ± 0.30.

The group comprising infants fed on heated breast milk shows no difference in bifidum count between full-term and premature infants, so that in this respect it may be regarded as homogeneous.

Table 24

Survey of Bifidum Counts in Different Dietary Groups

Group	Table	n	Range Millions per 1 g Faeces	Values %		Geometrical Mean Value Millions per 1 g (Logarithmic)
				<10 000	>10 000	
Breast-fed	3	46	1 100–153 000	10	90	32 000 (10.5±0.065)
Fed on heated breast milk						
Full term.....	6	28	240– 25 000	93	7	3 200 (9.5±0.084)
Prematures ...	7	18	170– 15 000	94	6	2 500 (9.4±0.11)
Bottle-fed	13	34	<100– 28 000	75	25	4 000 (9.6±0.11)
Fed on mixed diets	18					
≦ 1 year.....		18	< 10– 36 000	67	33	4 000 (9.6±0.20)
1–12 »		18	< 10– 6 100	100	—	500 (8.7±0.22)

Table 25

Survey of Number of Bacteria Growing on Dextrose Agar in Different Dietary Groups

Group	Table	n	Range Millions per 1 g Faeces	Values %		Geometrical Mean Value Millions per 1 g (Logarithmic)
				<1 000	>1 000	
Breast-fed ...	3	45	< 1– 5 000	74	26	160 (8.2±0.16)
Fed on heated breast milk						
Full term.....	6	28	30– 7 600	60	40	800 (8.8±0.11)
Prematures ...	7	18	162– 8 400	33	67	1 300 (9.1±0.12)
Bottle-fed	13	34	13–18 300	35	65	1 600 (9.2±0.11)
Fed on mixed diets	18					
≦ 1 year		18	6– 3 200	72	28	400 (8.6±0.15)
1–12 »		18	4– 3 400	83	17	63 (7.8±0.26)

Table 26

Faecal pH Values in Different Dietary Groups

Group	Table	Distribution in the Group	pH Values in Per Cent		Odour of Faeces Per cent	
			<7	>7	Acid	Faecal
Breast-fed	3	4.2–8.3	93	7	92	8
Fed on heated breast milk						
Full term.....	6	4.5–6.7	100	—	93	7
Prematures	7	4.9–6.3	100	—	94	6
Bottle-fed	13	5.1–8.7	20	80	—	100
Fed on mixed diets	18					
≦ 1 year.....		5.5–8.4	44	56	—	100
1–12 »		6.3–9.1	56	44	—	100

Most of the infants were aged from ten days to one month, and all of them were fed from birth solely on heated breast milk. The bifidum count in this group does not exceed 25 000 million per gramme faeces, and thus approximates to that in the bottle-fed infants. A difference similar to that between breast-fed infants and infants fed on heated breast milk emerged in the investigations of infants who had changed from breast feeding to feeding with heated breast milk and vice versa; the change in the bifidum count was found to be reversible and proceeded in both directions within the course of a few days up to one week.

The bifidum count in breast-fed and in bottle-fed infants was not dependent on the period during which the infant had a uniform diet. The situation was different in principle with regard to feeding on heated breast milk. Eight full-term infants were followed up over a period of several months, the bifidum count being found to increase progressively between the first and second month, so that values of 30 000 to 80 000 million per gramme were attained; *i.e.* they approximated to those in

the breast-fed infants. Infant M. H., with a final value of about 15 000 million per gramme, was an exception. In the full-term infants this rise consistently occurred in the manner described; in the premature infants it started earlier and proceeded more rapidly in certain cases, but in others it still showed no signs of having commenced after seven weeks.

Due to practical difficulties no attempts were made to study quantitatively the other bacterial flora in the investigated samples of faeces. To facilitate a certain quantitative comparison between *Bact. bifidum* and other bacteria in the flora, regular counts were made of bacteria growing on endoagar and 2 per cent dextrose agar, in addition to the bifidum cultures. These two groups are collectively designated "other bacteria" (see page 11).

The number of other bacteria, in this comparison represented by those growing on dextrose agar, was lower in breast-fed infants than in infants who were not breast fed. The differences between the logarithmic mean value of the group comprising breast-fed infants and the logarithmic mean values of each of the two following groups are significant ***, the differences being —0.8 $\pm$ 0.18 (infants mainly under one month fed on heated breast milk), and —1.0 $\pm$ 0.19 (bottle-fed infants). No significant difference exists between the logarithmic mean values in respect of breast-fed infants and that in respect of each age group fed on mixed diets.

The children over one year who were fed on mixed diets showed a lower number of other bacteria than the infants fed on heated breast milk and the bottle-fed infants. The differences between the logarithmic mean value of the first-named group and that of each of the last-named groups are significant ***, the differences being

—1.2 $\pm$ 0.27 (infants mainly under one month fed on heated breast milk)
—1.4 $\pm$ 0.28 (bottle-fed infants).

The breast-fed infants are thus characterized by higher bifidum counts than those found in any other form of feeding,

and by a low number of other bacteria. The ratio between the mean values is in the region of 100 to one. In most infants the faeces had a pH below 7 and an acid odour. If breast-fed infants were changed to heated breast milk or to bottle feeding, the bifidum count decreased by about 90 per cent to roughly one-tenth of the previous values. Concurrently the number of other bacteria increased, so as to make the ratio between the mean values between two and four to one. In the former case the pH and odour of the faeces remained unchanged; in the latter case they were over 7 and faecal respectively. If the new mode of feeding was continued, *Bact. bifidum* adapted itself, in feeding on heated breast milk, to the new conditions in the bowel and progressively rose to levels approximating to those found in breast-fed infants. After some time, but not coincidentally with the above, the pH rose (to around or over 7) and the odour became faecal in some cases. But with continued bottle feeding, on the other hand, no change occurred either in the bifidum count or in the pH and odour of the faeces.

As regards the bifidum count during weaning itself, the investigation showed that it did not fall proportionally with the amount of breast milk, but that it might be unchanged in principle as long as the daily amount of milk taken direct from the breast exceeded approximately 200 grammes. In this connection the nature of the supplementary food seemed to be only of minor importance. In general it appeared that the low pH levels shown by the breast-fed infants could not be maintained during weaning if the amount of breast milk fell to less than 400 g per day.

On continued feeding on mixed diets, the bifidum count was unchanged during the year of infancy, whereas the number of other bacteria showed a tendency to decline. (The difference in this respect between bottle-fed infants and infants fed on mixed diets was significant **.) After the age of one year the bifidum count too showed a tendency to fall (the difference being significant ** between children under and over one year in the mixed diet group). However, both an age factor and a dietary factor must be reckoned with here. For instance, there is more

cow's milk in the mixed diet of infants under 1 year than in that of children over 1 year.

The investigation shows in many ways that *Bact. bifidum*, though markedly acid-forming, is not of major significance relative to the pH in the colon and hence in the faeces. For example, infants fed on heated breast milk, at all events during the first month of life, showed the same pH as breast-fed infants, but on the average only 10 per cent of the latter's bifidum count. The consistently observed rise in the bifidum count during prolonged feeding on heated breast milk proceeded even when the pH in some infants rose to values over seven. When such an infant was subsequently treated with aureomycin or chloromycetin, the pH fell coincidentally with a decrease of 90 per cent or more in the bifidum count.

The variations in the pH of the faeces, which were observed in the infants fed on heated breast milk, can probably be explained as follows.

Those constituents of breast milk which, on being affected by the bacterial processes in the intestine, give rise to the low pH and acid odour typical of the breast-fed infant, undergo certain changes when the breast milk is heated. These changes are of such nature that in certain infants the bacterial activity in the bowel is gradually shifted from the side of acid-forming processes toward those that give rise to bases. The almost entirely fermentative flora of the healthy breast-fed infant is replaced by a mixed flora which includes putrefactive bacteria. The result is reflected in a rise in the pH of the faeces to between 6 and 7 or more, the odour at the same time becoming faecal.

By treatment with aureomycin and chloromycetin in these cases, the intestinal processes are influenced in such a way that the pH falls and the odour becomes acid or indifferent. It would seem that these antibiotics have a relatively stronger effect on the putrefactive flora in the bowel than on the normal fermentative flora, thereby shifting the bacterial status toward that found in breast-fed infants.

The above-described spontaneous rises in the pH values on prolonged feeding with heated breast milk occurred, as mentioned

before, only in certain of the infants. In others a low pH and an acid odour were maintained in the same way as in a purely breast-fed infant. When these infants were treated with aureomycin or chloromycetin, the pH tended to rise while the odour became less acid or indifferent (the chloromycetin treatment of infant M. O. is an exception). In these cases it seems plausible to attribute this neutral trend of the pH and odour to a lowered acid production caused by inhibition of the existing fermentative flora.

The possibility cannot be precluded, of course, that the substantial decrease of *Bact. bifidum* in these cases contributed in some degree to the change in the pH. Yet on the other hand the relevant conditions in infants S. H. and H. Z. suggest that the number of bifidum bacteria cannot demonstrably influence the pH and odour of the faeces.

The other bacterial flora found in these investigations presented no changes worthy of note coinciding with those in the pH level.

Conclusions

1. *Bact. bifidum* occurs both in breast-fed infants and in infants not fed on breast milk.

2. The bifidum count is higher in breast-fed infants than in infants not fed on breast milk, the difference being statistically significant ***.

3. The bifidum-stimulating property of breast milk will be lost if such milk is heated to a temperature of 100° C or pasteurised at 68° C for 10 minutes. The difference with respect to breast-fed infants and infants fed on heated breast milk during the first month is statistically significant ***.

4. If an infant is fed on heated breast milk, *Bact. bifidum* will adapt itself to conditions in the bowel and after one to two months will increase progressively to the level occurring in breast-fed infants. This rise in the bifidum count proceeds both in full-term and in premature infants, though not with the same regularity in the latter.

5. Examination of infants at different ages and at different

stages of weaning seems to show that a bifidum count corresponding in principle to that found in breast-fed infants may occur as long as the amount of breast milk suckled daily exceeds approximately 200 grammes.

6. The number of "other bacteria" is lower in breast-fed than in bottle-fed infants of the same age. The difference, calculated on the number of bacteria growing on dextrose agar, is statistically significant ***.

7. The number of "other bacteria" is lower in breast-fed infants than in infants of the same age fed on heated breast milk. The difference, calculated on the number of bacteria growing on dextrose agar, is statistically significant ***.

8. A close correlation exists between the pH and the odour of the faeces. pH values lower than 6 are attended by an acid odour, and pH values higher than 7 by a faecal odour. pH 6 and 7 are borderline values between which the conditions vary.

9. *Bact. bifidum* appears to be of very little significance relative to the pH of the faeces. This is indicated, for instance, by the fact that heated breast milk initially gives the same pH as milk suckled direct from the breast, but only 10 per cent of the number of *Bact. bifidum* associated therewith.

10. No correlation seems to exist between the bifidum count and the number of "other bacteria", either in breast-fed or in bottle-fed infants.

11. Both alpha and beta lactose, when administered by mouth to children between the ages of one month and two years, seem to be capable of producing in certain cases a moderate increase in the bifidum count. The increase is not significant. No difference has been found in this respect between alpha and beta lactose.

12. The bifidum count and the number of "other bacteria" are lower in children over one year fed on mixed diets than in bottle-fed infants. The difference in each case is statistically significant ***.

13. *Bact. bifidum* is markedly inhibited *in vivo* by aureomycin and chloromycetin. With a dose of approximately 40 mg per

kilogramme body weight per day, the bifidum count decreases by 90 per cent or more.

14. *Bact. bifidum* is inhibited *in vivo* by penicillin. With an unchanged dose per day the effect appears to be stronger in oral than in parenteral (intramuscular) administration.

15. *Bact. bifidum* is completely inhibited *in vitro* by

Sulphonamide (Elkosin) in a concentration of 3.3 mg but not 1.32 mg per millilitre;

Penicillin in a concentration of 1 unit but not 0.25 units per millilitre;

Streptomycin in a concentration of 50 mg but not 10 mg per millilitre.

Schlussfolgerungen

1. Bact. bifidum findet sich bei sowohl Brustkindern wie Kindern ohne Brustmilch.

2. Die Bifidumzahl ist bei den ersteren höher als bei den letzteren. Der Unterschied ist signifikant ***.

3. Die bifidumstimulierende Eigenschaft der Brustmilch verschwindet, wenn die Milch mit Wärme behandelt wird (Erhitzen auf 100° oder 10 Minuten langes Pasteurisieren bei 68°). Der Unterschied zwischen Brustkindern und Kindern, die mit Wärme behandelte Milch erhalten, ist während des ersten Monats signifikant ***.

4. Bei Ernährung mittels mit Wärme behandelter Brustmilch passt sich das Bact. bifidum den Verhältnissen im Darm an und vermehrt sich schrittweise nach 1—2 Monaten, um das Brustkinderniveau zu erreichen. Dieser Anstieg der Bifidumzahl erfolgt bei sowohl ausgetragenen wie frühgeborenen Kindern, bei den letzteren jedoch nicht mit derselben Regelmässigkeit.

5. Die Untersuchung von Säuglingen verschiedenen Alters und während verschiedener Phasen der Entwöhnung scheint ersichtlich zu machen, dass die Bifidumzahl im Prinzip ebenso wie bei Brustkindern sein kann, so lange die täglich zugeführte Brustmilchmenge ca. 200 g übersteigt.

6. Die Zahl der „übrigen Bakterien" ist bei Brustkindern niedriger als bei gleichaltrigen Flaschenkindern. Der Unterschied,

nach Massgabe auf Dextroseagar wachsender Bakterien berechnet, ist signifikant ***.

7. Die Zahl der „übrigen Bakterien" ist bei Brustkindern niedriger als bei gleichaltrigen, mittels mit Wärme behandelter Brustmilch ernährten Kindern. Der Unterschied, nach Massgabe auf Dextroseagar wachsender Bakterien berechnet, ist signifikant ***.

8. Es besteht eine enge Wechselbeziehung zwischen pH-Wert und Geruch des Stuhls. Ein pH-Wert < 6 geht mit einem säuerlichen, ein pH-Wert > 7 mit einem fäkalen Geruch Hand in Hand. Zwischen 6 und 7 liegt ein Grenzgebiet, in dem das Verhalten wechselt.

9. Die Bedeutung des Bact. bifidum für die Wasserstoffionenkonzentration des Stuhls scheint sehr gering zu sein. Hierfür spricht u. a. der Umstand, dass mit Wärme behandelte Brustmilch anfangs dieselbe Wasserstoffionenkonzentration bewirkt wie unbehandelte Brustmilch, aber nur 10 % der Bifidumzahl der letzteren.

10. Anscheinend besteht keine Wechselbeziehung zwischen der Bifidumzahl und der Zahl „übriger Bakterien", und zwar weder bei Brust- noch Flaschenkindern.

11. Sowohl α- wie β-Laktose scheint bei peroraler Zufuhr bei Kindern im Alter 1 Monat—2 Jahre in gewissen Fällen einen mässigen Anstieg der Bifidumzahl bewirken zu können. Die Zunahme ist nicht signifikant. Ein Unterschied in bezug auf die bifidumstimulierende Wirkung hat sich zwischen α- und β-Laktose nicht ergeben.

12. Die Bifidumzahl und die Zahl „übriger Bakterien" sind bei Kindern über 1 Jahr mit gemischter Kost niedriger als bei Flaschenkindern. Beide Differenzen sind signifikant ***.

13. In vivo wird das Bact. bifidum von Aureomycin und Chloromycetin stark gehemmt. Bei einer Dosis von ca. 40 mg pro kg Körpergewicht und Tag sinkt die Bifidumzahl um 90 % oder mehr.

14. In vivo wird das Bact. bifidum von Penicillin gehemmt. Bei gleicher Tagesdosis scheint perorale Verabreichung in dieser Beziehung stärker zu wirken als parenterale (intramuskuläre Injektion).

15. In vitro wird das Bact. bifidum völlig gehemmt von:

Sulfonamid (Elkosin) in Konzentration 3.3 mg/ml, nicht aber 1.32 mg/ml
Penicillin in Konzentration 1 Einh./ml, nicht aber 0.25 Einh./ml
Streptomycin in Konzentration 50 mg/ml, nicht aber 10 mg/ml.

Conclusions

1. La bact. bifidum se rencontre aussi bien chez les nourrissons que chez les enfants non nourris à la mamelle.

2. Le nombre des bact. bifidum chez les nourrissons est plus élevé que chez les enfants non nourris à la mamelle. La différence est significative ***.

3. La propriété du lait de femme stimulant les bact. bifidum se perd lorsque ce lait est chauffé à une température de 100° ou bien pasteurisé à 68° durant 10 minutes. La différence entre les nourisssons et les enfants nourris, pendant le premier mois, de lait de femme chauffé est significative ***.

4. Lorsque l'enfant est nourri de lait de femme chauffé, la bact. bifidum s'adapte aux conditions dans l'intestin et s'accroît dans 1 à 2 mois successivement jusqu'au niveau que l'on trouve chez les nourrissons. Un tel accroissement du nombre des bifidum se produit tant chez des enfants nés à terme que chez ceux nés avant terme, cependant non avec la même régularité chez ces derniers.

5. L'examen de bébés à différents âges et stades de sevrage paraît indiquer qu'un nombre de bact. bifidum correspondant en principe à celui que l'on trouve chez les nourrissons, peut se présenter aussi longtemps que la quantité de lait de femme absorbé journellement excède environ 200 gr.

6. Le nombre "d'autres bactéries" chez les nourrissons est inférieur à celui existant chez les bébés du même âge nourris au biberon. La différence entre le nombre de ces bactéries et celui des bactéries cultivées dans du agar-dextrose est significative ***.

7. Le nombre des "autres bactéries" chez les nourrissons est inférieur à celui existant chez les bébés du même âge nourris avec du lait de femme chauffé. La différence entre le nombre de

ces bactéries et celui des bactéries dans du agar-dextrose est significative ***.

8. Il existe une corrélation intime entre la valeur pH et l'odeur des féces. La valeur pH < 6 est accompagnée d'une odeur acide, tandis que pH > 7 est accompagnée d'une odeur fécale. La valeur pH 6—7 représente une marge en-dedans de laquelle varient les conditions.

9. L'effet de la bact. bifidum sur la valeur pH des féces semble être minime. Ceci est, entre autres, confirmé par le fait que le lait de femme chauffé donne initialement la même valeur pH que le lait de femme absorbé directement, tandis que le nombre des bifidum ne représente que 10 % de ce dernier.

10. Il ne paraît pas exister de corrélation entre le nombre des bifidum et celui des "autres bactéries", ni chez les nourrissons, ni chez les enfants nourris au biberon.

11. La lactose α, aussi bien que la lactose β paraissent pouvoir, étant administrées péroralement à des bébés de 1 mois à 2 ans, produire dans certains cas un accroissement modéré du nombre des bifidum. Cet accroissement n'est pas significatif. Aucune différence dans l'effet stimulant sur les bifidum entre la lactose α et la lactose β ne s'est manifestée.

12. Le nombre des bifidum et celui des "autres bactéries" chez les bébés ayant dépassé l'âge d'un an et nourris d'aliments mélangés est inférieur à celui des enfants nourris au biberon. Les deux différences sont significatives ***.

13. La bact. bifidum est in vivo efficacement combattue par l'auromycine et la chloromycétine. Par une dose d'environ 40 mg par 1 kg de poids du corps et par jour, le nombre des bifidum se trouve diminué de 90 % ou davantage.

14. La bact. bifidum est in vivo combattue par la pénicilline. L'effet en paraît être, au mêmes doses journalières, plus grand lors d'une administration pérorale que lors d'injections intra-musculaires.

15. La bact. bifidum est in vitro entièrement enrayée par
la Sulfonamide (Elkosin) concentrée de 3.3 mg/ml, mais non à 1.32 mg/ml
la Pénicilline concentrée de 1 E/ml, mais non à 0.25 E/ml
la Streptomycine concentrée de 50 mg/ml, mais non à 10 mg/ml.

Conclusiones

1. Las bact. bifidum se dan tanto en el intestino de los niños criados al pecho como en el de los alimentados en otra forma.

2. El número de bact. bifidum es mayor en los niños criados al pecho que en los alimentados de otra manera, siendo considerable la diferencia ***.

3. La propiedad estimuladora de la formación de las bact. bifidum de la leche materna desaparece si se calienta ésta hasta una temperatura de 100° o si se la pasteuriza a 68° C durante 10 minutos. La diferencia entre los niños criados al pecho y los alimentados con leche materna calentada durante el primer mes es considerable ***.

4. Cuando un niño se cría con leche materna calentada, las bact. bifidum se adaptan a las condiciones en el intestino, aumentando sucesivamente al cabo de 1—2 meses hasta alcanzar el mismo nivel que en los niños criados al pecho. Este aumento de bact. bifidum se produce tanto en los niños a término como en los prematuros, si bien no con la misma regularidad en estos últimos.

5. Los exámenes de los niños de diferentes edades y en diferentes fases del destete parecen mostrar que puede encontrarse un número de bact. bifidum igual, en principio, al que presentan los niños criados al pecho, siempre que la cantidad de leche materna ingerida diariamente sea superior a unos 200 gramos.

6. El número de las "demás bacterias" es menor en los niños criados al pecho que en los de la misma edad criados con biberón. La diferencia, calculada por el número de bacterias en cultivos de agar-dextrosa, es considerable ***.

7. El número de las "demás bacterias" es menor en los niños criados al pecho que en los de la misma edad criados con leche materna calentada. La diferencia, calculada por el número de bacterias en cultivos de agar-dextrosa es considerable ***.

8. Existe una estrecha correlación entre el pH y el olor de los excrementos. En pH inferiores a 6 se observa un olor ácido y en pH superiores a 7 un olor fecal. Los valores de 6 a 7 son limítrofes, en que las condiciones varían.

9. La importancia de las bact. bifidum para el pH de los excrementos parece ser muy escasa. Esto se desprende, entre otras cosas, del hecho de que, inicialmente, la leche materna calentada da el mismo pH que la ingerida directamente del pecho, pero sólo el 10 % del número de bact. bifidum de ésta.

10. No parece existir correlación entre el número de bact. bifidum y el de las "demás bacterias", ni en los niños criados al pecho ni los criados con biberón.

11. Tanto la lactosa alfa como la beta, administrada per os a niños de un mes a dos años de edad parece poder producir en ciertos casos un aumento moderado del número de bact. bifidum. El aumento no es considerable. No se ha comprobado ninguna diferencia a este respecto entre la lactosa alfa y beta.

12. El número de bact. bifidum y de "otras bacterias" es menor en los niños de más de un año que reciben alimentación mixta que en los criados con biberón. Ambas diferencias son considerables ***.

13. In vivo las bact. bifidum son inhibidas acentuadamente por la aureomicina y la cloromicetina. Con una dosis diaria de unos 40 mg por kilogramo de peso corporal el número de bact. bifidum disminuye en 90 % o más.

14. In vivo las bact. bifidum son inhibidas por la penicilina. Con una dosis diaria igual, el efecto parece ser mayor si se administra por vía oral que parenteral (intramuscular).

15. In vitro las bact. bifidum son inhibidas completamente por:

Sulfonamidas (Elkosin) de una conc. de 3.3 mg/ml pero no de 1.32 mg/ml;
Penicilina de una conc. de 1 unidad por ml pero no de 0.25 un./ml
Estreptomicina de una conc. de 50 mg/ml pero no de 10 mg/ml.

Table 27

Infants Fed on Heated Breast Milk, Submitted to Serial Tests and Treated with Antibiotics by Mouth and Intramuscularly
(Explanatory Notes, see Page 83)

Date	Faeces		Millions of Bacteria per 1 g of Faeces			Remarks
	Odour	pH	Coliform	Growing on Dextrose Agar	Bact. Bifidum	
M. O. Born 11.3. Fig. 32						
27.3	A	6.1	720	2 480	< 100	
1.4	»	5.0	456	600	4 680	
13.4	»	5.4	1 100	1 130	27 000	
17.4	»	5.4	395	580	6 000	
24.4	»	5.8	15	79	5 200	
2.5	»	5.0	98	380	20 000	
17.5	»	5.5	1 070	1 980	30 400	
19.5	»	4.8	129	123	29 000	
24.5	»	5.4	620	1 180	68 400	Non-heated breast
26.5	»	5.1	< 1	< 1	28 000	milk 19–26.5
30.5	»	5.1	3 000	3 000	< 10	Chloromycetin
1.6	»	5.2	3 430	3 560	20	26.5–1.6
3.6	»	5.1	149	510	21 000	
8.6	»	5.4	1 150	4 100	76 300	
12.6	O	7.1	6 600	17 000	< 100	Aureomycin 9–14.6
13.6	»	6.5	< 1	< 1	< 100	
14.6	»	6.3	160	< 1	< 100	
19.6	(A)	5.3	156	45	33 000	
21.6	A	5.0	67	41	54 000	
A. Z. Born 9.12. Fig. 33						
27.12	(F)	6.3	5 500	7 600	1 800	
16.1	A	5.4	300	150	250	
30.1	»	4.4	69	57	35 000	
1.2	»	5.4	720	1 000	30 000	
4.2	»	4.8	820	820	12 000	Streptomycin 1–8.2
7.2	»	5.0	< 1	< 1	26 000	
8.2	»	4.9	610	1 020	19 000	

(Table 27 cont.)

Date	Faeces		Millions of Bacteria per 1 g of Faeces			Remarks
	Odour	pH	Coliform	Growing on Dextrose Agar	Bact. Bifidum	
13.2	A	5.2	58	59	30 000	
20.2	»	6.4	1	5 360	< 100	Aureomycin 16–21.2
21.2	O	6.4	2	4 370	< 100	
25.2	A	5.6	165	3 170	25 000	
6.3	»	5.7	470	2 060	< 100	Non-heated breast
8.3	»	4.4	1	2 520	6 100	milk 25.2–16.3
9.3	»	5.3	430	780	43 000	
11.3	(A)	5.9	340	4 100	450	Chloromycetin
13.3	(A)	6.5	227	9 700	< 100	9–16.3
14.3	O	7.2	199	8 300	< 100	
21.3	(F)	5.1	64	204	55 000	
	T. F. Born 1.1. Fig. 34					
6.3	—	6.4	580	810	4.230	
17.2	A	5.3	931	1 190	22 500	
27.2	F	5.8	172	269	6 900	
6.3	»	6.1	200	5 500	43 000	
16.3	A	5.3	1 950	7 100	< 100	Aureomycin 13–20.3
20.3	»	4.5	1	15	7 400	
22.3	O	6.8	93	> 30 000	< 100	
24.3	A	5.2	11 500	11 100	29 400	
28.3	»	4.9	2 080	1 590	33 000	Chloromycetin
29.3	»	5.7	2 190	2 590	< 100	24–29.3
1.4	O	6.7	340	4.100	57 600	
	Å. S. Born 11.1. Fig. 35					
8.3	A	5.2	102	1 140	1 320	
16.3	O	4.5	20	64	36 000	
28.3	»	6.2	244	1 450	17 000	
30.3	F	5.9	360	> 30 000	< 100	Aureomycin
1.4	»	7.9	1 700	20 800	1 500	28.3–1.4

(Table 27 cont.)

Date	Faeces		Millions of Bacteria per 1 g of Faeces			Remarks
	Odour	pH	Coliform	Growing on Dextrose Agar	Bact. Bifidum	
22.4	F	7.8	205	1 850	48 000	
29.4	A	7.5	27	7 000	76 000	
4.5	»	5.0	180	1 690	< 100	Chloromycetin 1–8.5
6.5	»	6.2	2 750	18 000	< 100	
8.5	»	6.2	4 310	8 700	< 100	
17.5	—	7.7	550	1 740	90 000	
24.5	(F)	7.6	750	990	12 600	
3.6	F	7.6	152	380	43 300	Non-heated breast milk 26.5–3.6
K. N. Born 4.1. Fig. 36						
21.1	A	6.6	100	200	1 890	
6.2	»	5.4	130	10	290	
13.2	»	5.2	2	28	16 000	
21.2	»	5.1	41	333	3 160	
4.3	(F)	7.2	410	—	25 200	
9.3	»	6.7	390	2 660	34 200	
14.3	»	7.5	141	1 590	26 100	
17.3	A	5.3	202	9 500	< 100	Aureomycin 14–20.3
18.3	(A)	5.3	123	35 100	< 100	
20.3	»	6.9	20	> 30 000	< 100	
19.4	F	6.8	690	1 360	1 390	Entirely bottle-fed since 14.3
H. N. Born 14.4						
27.4	A	5.1	1 980	2 400	3 000	
6.5	»	5.3	732	8 000	2 800	
16.5	O	5.4	520	1 830	< 100	Aureomycin 11–15.5
M. H. Born 20.1. Fig. 37						
8.2	A	5.2	1 940	2 520	800	
18.2	»	4.9	2 060	2 020	3 010	
24.2	»	5.0	93	243	1 300	

(Table 27 cont.)

Date	Faeces		Millions of Bacteria per 1 g of Faeces			Remarks
	Odour	pH	Coliform	Growing on Dextrose Agar	Bact. Bifidum	
2.3	A	5.4	179	480	270	
9.3	»	5.4	214	231	13 000	
15.3	»	4.2	< 1	23	8 400	
16.3	»	5.2	189	990	13 500	
21.3	»	5.2	< 1	7	710	
28.3	»	6.5	1 640	3 900	< 100	Aureomycin 23–29.3
29.3	O	6.2	125	1 700	< 100	
22.4	A	4.9	1 330	1 220	21 000	
24.4	»	5.5	600	1 090	12 500	
26.4	O	6.0	< 1	1 800	< 100	Chloromycetin
27.4	(A)	5.9	18	2 170	900	24–29.4
28.4	O	5.6	170	540	4 950	
29.4	(A)	5.4	830	6 400	2 000	
2.5	A	5.6	227	560	21 000	
8.5	»	5.3	228	211	7 500	
13.5	O	5.2	52	72	70	Penicillin per os
16.5	A	5.5	800	1 090	10 500	11–27.5
19.5	»	5.1	350	550	7 500	
25.5	»	4.7	141	136	3 200	
27.5	»	6.1	730	2 800	< 100	
3.6	O	4.5	29	34	< 100	Non-heated breast
8.6	A	5.1	3	50	13 000	milk 3–8.6
14.6	»	5.3	70	34	17 000	
S. H. Born 20.11. Fig. 38						
15.12	A	5.1	940	1 470	980	
19.12	O	6.5	4 100	5 100	10 800	
4.1	F	6.4	2 400	2 700	40 000	
13.1	(F)	7.6	1 030	2 160	31 500	
19.1	»	6.3	106	—	< 100	Aureomycin 12–19.1
27.1	»	7.7	1 370	2 090	57 600	
3.2	»	7.6	1 020	3 090	63 000	

(Table 27 cont.)

Date	Faeces		Millions of Bacteria per 1 g of Faeces			Remarks
	Odour	pH	Coliform	Growing on Dextrose Agar	Bact. Bifidum	
6.2	A	5.4	230	2 350	32 000	Aureomycin 3–8.3
8.2	(A)	6.7	188	1 520	4 400	
14.2	A	6.0	690	1 220	13 200	
21.2	F	7.7	92	910	45 600	Non-heated breast
25.2	(F)	7.7	300	2 710	92 000	milk 15–25.2
3.3	»	6.4	142	1 600	72 000	
6.3	»	7.7	< 1	2 220	500	Chloromycetin 3–9.3
7.3	A	5.2	700	2 000	< 100	
8.3	»	5.7	1 890	9 500	< 100	
9.3	»	5.4	340	2 840	28 800	
14.3	(F)	7.6	129	3 500	53 200	
17.3	»	7.1	2	4 200	16 000	
20.3	F	7.9	84	1 370	32 000	Penicillin per os
27.3	»	7.4	520	620	28 800	18–29.3
29.3	»	7.8	195	600	20 700	
1.4	»	7.1	810	4 600	82 800	
12.4	»	7.6	295	560	12 600	
18.4	(A)	5.4	102	108	7 520	Streptomycin
21.4	F	7.6	181	550	1 560	15–22.4
22.4	»	8.2	152	1 780	3 750	
26.4	»	5.2	4	180	10 800	
G. L. Born 9.10						
17.10	(A)	5.7	54	72	4 550	
23.10	F	6.0	900	1 490	435	Penicillin per os 18–23.10
A. N. Born 8.9						
23.10	A	5.5	3 410	2 890	5 200	
24.10	»	5.7	260	2 390	1 500	

(Table 27 cont.)

Date	Faeces		Millions of Bacteria per 1 g of Faeces			Remarks
	Odour	pH	Coliform	Growing on Dextrose Agar	Bact. Bifidum	
28.10	A	5.9	3 920	5 000	< 100	Penicillin per os
31.10	»	6.3	1 750	7 200	6 750[1]	25.10–4.11
8.11	»	5.6	< 1	85	315	
E. N. Born 21.8						
14.9	A	5.3	221	420	7 000	
21.9	»	5.8	2 500	4 900	2 250	Penicillin procaine
25.9	»	5.6	350	500	1 350	16–26.9
28.9	O	7.2	< 1	20	50	Aureomycin
4.10	»	6.4	< 1	4 900	340	25.9–8.10
7.10	»	6.7	< 1	6 600	< 100	
11.10	»	6.0	5	5 600	< 100	
14.10	A	6.1	1 240	8 500	< 100	
20.10	(F)	6.1	910	1 900	38 000	
24.10	F	5.6	730	1 270	13 500	
27.10	»	6.0	1 820	1 660	738	Penicillin intramusc.
31.10	»	5.8	520	1 700	783	24–31.10
10.11	»	5.7	6	1 500	153	
15.11	»	5.9	13	1 730	3 680	Penicillin per os
17.11	»	5.6	< 1	600	2 440	8–17.11
M. B. Born 16.9. Birth weight 1 640 g						
12.10	F	5.8	2 930	4 500	2 070	
16.10	»	5.8	1 260	2 160	480	
20.10	(F)	5.7	3 000	6 200	200	Penicillin intramusc.
25.10	F	6.2	1 550	2 570	8 100[2]	16–27.10
26.10	»	6.0	1 590	2 400	3 400[2]	
2.11	»	5.8	< 1	120	70 000	

[1] Bifidum bacteria atypical and, in part, affected by toxin.
[2] Bifidum bacteria affected by toxin.

(Table 27 cont.)

Date	Faeces		Millions of Bacteria per 1 g of Faeces			Remarks
	Odour	pH	Coliform	Growing on Dextrose Agar	Bact. Bifidum	
P. Ö. Born 2.8						
3.10	A	5.8	112	230	8 100	
5.10	»	5.8	143	380	31 000	
10.10	»	6.2	336	1 020	< 10	Penicillin per os
14.10	(A)	6.0	930	1 710	< 10	5–17.10
17.10	A	6.2	1 480	2 050	410	
19.10	»	6.2	1 180	2 910	240	
21.10	»	5.8	960	1 770	31 000	
26.10	»	5.3	430	860	16 000	Penicillin intramusc.
30.10	»	5.3	930	2 230	9 600	23–30.10

Table 28

Nine-Year-Old Girl (M.R.) Treated with Aureomycin

Date	Faeces		Millions of Bacteria per 1 g of Faeces			Remarks
	Odour	pH	Coliform	Growing on Dextrose Agar	Bact. Bifidum	
13.9	F	6.8	1	2	2 500	Mixed diet
30.9	(F)	8.1	2 860	3 690	310	Aureomycin 18–30.9

Table 29

Bottle-Fed Infants Given Alpha and Beta Lactose as a Substitute for Sucrose or Glucose (Group 1)

Date	Faeces pH	Millions of Bacteria per 1 g of Faeces			Diet
		Coliform	Growing on Dextrose Agar	Bact. Bifidum	
L. B. Born 26.3. Fig. 12					
31.3	5.4	60	460	1 200	Heated breast milk
1.4	5.3	40	280	2 700	» » »
4.4	5.4	3 000	3 900	5 040	Citric acid milk with glucose since 3.4
8.4	5.3	6 300	8 600	1 200	β-lactose 5–9.4
9.4	4.8	1 100	4 100	4 200	
20.4	5.3	2 700	3 300	12 000	
21.4	5.7	2 000	4 700	5 600	
23.4	5.6	2 000	2 400	17 500	α-lactose 22–27.4
25.4	5.5	700	6 000	17 000	
27.4	5.8	4 000	4 300	1 850	
30.4	5.8	2 200	2 660	880	
2.5	5.8	19 000	14 000	14 000	
6.5	6.6	3 500	4 500	< 100	β-lactose 3–12.5
7.5	6.8	5 000	20 000	4 800	
9.5	7.2	3 100	8 000	12 600	
12.5	5.5	7 600	10 200	8 000	
16.5	7.3	7 000	9 000	10 500	
18.5	7.5	4 000	12 000	13 600	
P. O. Born 13.4					
22.4	5.5	560	670	6 840	Heated breast milk
26.4	4.9	10	40	< 100	Citric acid milk with
30.4	5.7	4 800	5 500	< 100	glucose since 26.4
2.5	7.3	10 000	31 000	< 100	
5.5	6.4	1 100	9 700	—	β-lactose 3–9.5
7.5	5.8	3 600	3 800	1 890	
9.5	6.3	4 800	6 100	2 400	

(Table 29 cont.)

Date	Faeces pH	Millions of Bacteria per 1 g of Faeces			Diet
		Coliform	Growing on Dextrose Agar	Bact. Bifidum	
12.5	7.6	6 000	17 000	< 100	
14.5	7.5	15 000	35 000	< 100	
18.5	7.7	9 000	21 000	< 100	α-lactose 15–21.5
19.5	7.6	5 000	24 000	3 400	
21.5	5.4	6 600	12 800	< 100	
26.5	8.1	9 000	30 000	2 600	
28.5	7.3	11 000	18 000	9 000	β-lactose 27.5–7.6
1.6	8.3	16 000	20 000	< 100	
2.6	7.8	6 000	20 000	< 100	
7.6	8.0	250	340	< 100	
B. L. Born 6.4. Fig. 13					
23.4	5.4	600	710	2 000	Heated breast milk
26.4	5.3	670	700	3 700	Citric acid milk with
30.4	7.7	3 700	5 600	9 600	glucose since 26.4
2.5	8.1	2 900	4 500	< 100	
5.5	6.4	500	1 100	18 000	β-lactose 3–9.5
9.5	6.2	5 000	7 000	3 000	
12.5	8.0	800	800	2 600	
14.5	7.8	16 000	30 000	< 100	
17.5	8.1	6 700	9 600	11 000	α-lactose 15–21.5
19.5	6.7	3 300	5 000	1 590	
21.5	6.9	5 900	9 000	10 000	
26.5	8.1	15 000	30 000	< 100	
28.5	7.6	4 200	6 300	< 100	β-lactose 27.5–4.6
1.6	7.6	7 000	14 000	14 400	
2.6	5.6	3 000	3 000	2 520	
4.6	6.4	—	—	3 360	
A. O. Born 25.1. Fig. 14					
7.2	6.3	2 700	4 900	2 100	Heated breast milk 25–31.1
8.2	6.6	500	1 100	2 170	Heated breast milk 50 per cent 1–3.2
11.2	7.6	410	4 800	< 100	Citric acid milk with sucrose since 4.2

(Table 29 cont.)

Date	Faeces pH	Millions of Bacteria per 1 g of Faeces			Diet
		Coliform	Growing on Dextrose Agar	Bact. Bifidum	
14.2	5.5	3 600	3 300	640	β-lactose 12–18.2
15.2	7.7	2 000	4 600	< 100	
16.2	5.8	2 000	2 700	3 200	
17.2	7.0	610	1 260	11 400	
18.2	6.8	6 600	8 600	2 850	
19.2	6.9	4 000	6 000	< 100	
21.2	8.2	2 900	19 000	3 000	
23.2	7.0	3 500	5 500	4 000	
25.2	5.9	5 000	5 200	5 280	
4.3	5.4	2 400	2 500	4 680	α-lactose 3–16.3
7.3	5.5	12 000	14 000	15 200	
9.3	6.9	2 600	3 100	9 800	
11.3	6.1	4 100	5 500	19 600	
14.3	5.5	4 700	5 100	14 400	
16.3	7.4	4 900	6 400	28 000	
21.3	7.5	4 000	4 300	17 100	
23.3	7.7	5 400	7 000	21 000	
30.3	7.7	6 300	14 300	9 000	

Table 30

Bottle-Fed Infants Given Alpha and Beta Lactose as a Substitute for Sucrose (Group 2)

Date	Faeces pH	Millions of Bacteria per 1 g of Faeces			Diet
		Coliform	Growing on Dextrose Agar	Bact. Bifidum	
K. L. Born 9.6. Fig. 15					
28.9	8.8	2 400	4 260	14 000	Half-milk formula
30.9	8.3	191	347	28 000	
6.10	7.7	—	48	19 000	β-lactose 30.9–16.10
10.10	6.7	1	120	4 590	Temp. 38.4° 11–12.10
16.10	5.7	280	570	30 000	
21.10	6.3	240	740	8 400	
13.11	6.9	< 1	700	2 100	
22.11	6.7	12	1 200	42 000	α-lactose 14–28.11
28.11	6.2	116	1 300	63 000	
P. N. Born 9.5. Fig. 16					
15.9	8.1	23	45	22 000	Half-milk formula + small amounts of fruit a. potato purée
21.9	8.7	3	18	17 000	
29.9	8.3	1	25	95 000	β-lactose 21.9–8.10
4.10	6.4	28	279	25 000	
7.10	6.6	292	1 750	63 000	
9.10	—	43	1 350	66 000	
16.10	6.9	11	540	2 100	
30.10	6.3	43	1 300	19 000	
10.11	6.2	1	3 900	4 250	α-lactose 3–25.11 (except 14–17.11)
25.11	6.9	2	—	15 000	
K. Å. Born 2.8. Fig. 17					
11.0	6.2	9 200	11 100	1 200	Citric acid milk
12.9	6.2	4 000	4 300	5 700	
13.9	6.4	2 120	9 500	6 400	
19.9	8.0	7 700	9 600	1 000	β-lactose 14–27.9
25.9	5.7	4 600	5 100	3 800	

(Table 30 cont.)

Date	Faeces pH	Millions of Bacteria per 1 g of Faeces			Diet
		Coliform	Growing on Dextrose Agar	Bact. Bifidum	
D. I. Born 27.10. Fig. 18					
3.11	4.7	242	305	4 000	Heated breast milk
11.11	5.8	1 690	2 520	< 100	» » »
15.11	6.3	1 640	2 240	1 520	50 per cent
18.11	6.8	1 780	2 130	< 100	Citric acid milk since
22.11	7.8	4 580	500	< 100	15.11
29.11	8.3	2 580	3 250	< 100	
7.12	8.3	6 000	6 200	1 260	
11.12	6.3	2 700	3 300	2 900	α-lactose 8–14.12
13.12	7.9	10 600	14 800	2 800	
14.12	7.8	4 100	5 700	< 100	
15.12	6.5	5 300	5 900	< 100	
17.12	5.3	320	440	459	
18.12	8.4	3 300	5 200	9 000	
21.12	8.1	3 000	3 900	2 200	
31.12	8.0	3 000	3 600	4 800	
11.1	7.8	4 200	4 200	< 100	
9.2	7.6	< 1	420	1 400	
16.2	8.2	900	1 330	4 200	
9.3	8.4	2 500	3 300	15 300	
14.3	7.4	1 700	2 000	16 800	β-lactose 10–16.3
15.3	5.6	2 100	1 800	12 000	
16.3	7.4	1 700	1 700	36 000	
21.3	8.3	1 200	1 600	9 000	
23.3	8.1	700	700	22 500	

Table 31

Children Fed on Mixed Diets Plus Alpha and Beta Lactose (Group 3)

Date	Faeces pH	Millions of Bacteria per 1 g of Faeces			Remarks
		Coliform	Growing on Dextrose Agar	Bact. Bifidum	
Y. E. 7 Months. Fig. 19					
16.2	7.8	940	910	2 540	
21.2	7.4	415	800	6 900	
1.3	7.4	71	320	27 000	β-lactose 22.2–11.3
9.3	7.4	51	332	11 500	
11.3	7.6	860	—	22 500	
20.3	6.3	2	178	14 400	
22.3	7.5	< 1	740	9 000	
28.3	7.4	250	690	8 200	
27.4	7.7	140	560	10 200	
9.5	7.7	67	198	12 000	α-lactose 1–16.5
15.5	7.5	144	209	11 200	
16.5	7.8	73	186	30 000	
23.5	7.7	169	175	3 150	
9.6	7.7	168	258	4 000	
K. B. 8 Months. Fig. 20					
16.2	6.8	23	120	11 250	
21.2	7.8	< 1	6	6 100	
1.3	7.7	82	188	25 200	β-lactose 22.2–11.3
9.3	7.5	123	207	21 000	
11.3	7.4	1 010	—	29 700	
20.3	7.9	10	270	14 000	
23.3	7.9	36	9	11 000	
28.3	8.4	54	145	4 800	
27.4	8.3	7	225	20 000	
9.5	7.6	23	80	5 200	α-lactose 1–16.5
13.5	7.7	51	180	7 250	
16.5	7.3	46	—	26 000	
23.5	7.6	8	18	7 400	
9.6	6.7	1	20	22 000	

(Table 31 cont.)

Date	Faeces pH	Millions of Bacteria per 1 g of Faeces			Remarks
		Coliform	Growing on Dextrose Agar	Bact. Bifidum	
K. A. 13 Months. Fig. 21					
13.1	8.2	520	1 190	2 580	
14.1	8.4	240	1 110	8 400	
22.1	8.1	104	210	1 890	β-lactose 14–30.1
27.1	6.1	180	150	2 070	
30.1	7.5	48	57	20 000	
7.2	7.0	114	—	2 400	
15.2	5.8	45	140	1 200	
24.2	6.9	1	83	24 000	α-lactose 17.2–6.3
3.3	7.2	84	178	6 300	
6.3	6.0	16	67	3 500	
21.3	7.4	70	271	700	
U. J. 11 Months. Fig. 22					
21.10	6.2	1 200	7 400	880	
26.10	6.4	600	1 000	8 300	
31.10	6.6	1 600	1 890	2 340	β-lactose 26.10–11.11
8.11	6.7	1 230	1 250	3 150	
11.11	6.1	810	980	23 000	
22.11	7.7	350	610	3 500	
3.12	6.8	200	1 000	20 000	
12.12	7.8	2 700	3 500	3 600	α-lactose 4–19.12
16.12	6.8	2 100	2 800	26 400	
19.12	6.2	1 500	1 500	7 500	
P. W. 2½ Years. Fig. 23					
18.1	6.7	690	760	3 430	
19.1	6.7	105	365	3 270	
27.1	7.8	53	113	3 500	β-lactose 19.1–3.2
31.1	7.0	590	920	12 000	
3.2	7.5	86	102	400	

(Table 31 cont.)

Date	Faeces pH	Millions of Bacteria per 1 g of Faeces			Remarks
		Coliform	Growing on Dextrose Agar	Bact. Bifidum	
10.2	7.7	30	139	1 220	
15.2	7.1	101	159	459	
23.2	7.7	—	—	2 700	α-lactose 15.2–7.3
7.3	6.8	40	42	1 800	
18.3	8.1	—	1 100	1 050	
M. B. 2 Years. Fig. 24					
22.8	6.1	1 200	—	< 100	
31.8	6.0	500	1 200	840	
8.9	7.5	150	370	850	β-lactose 1–19.9
15.9	6.7	190	390	539	
19.9	6.6	660	800	1 200	
24.9	6.6	770	810	1 900	
3.10	7.6	430	430	650	
10.10	7.4	110	150	880	
17.10	7.8	31	40	2 100	α-lactose 11.10–2.11
27.10	7.0	20	30	1 500	
2.11	8.2	5	37	1 900	
11.11	7.3	—	—	—	
B. O. 11 Months. Fig. 25					
26.10	6.9	1 260	1 180	5 900	
31.10	7.7	2 500	4 500	13 950	β-lactose 26.10–11.11
8.11	8.0	630	650	33 000	
11.11	7.3	590	1 900	—	
22.11	7.2	340	640	3 150	
3.12	7.8	—	300	8 000	
12.12	8.1	1 390	1 650	—	α-lactose 4–20.12
16.12	6.6	2 130	2 330	8 000	
20.12	8.1	1 400	2 400	3 870	
28.12	8.5	515	660	3 650	

(Table 31 cont.)

Date	Faeces pH	Millions of Bacteria per 1 g of Faeces			Remarks
		Coliform	Growing on Dextrose Agar	Bact. Bifidum	
L. T. 9 Months. Fig. 26					
30.1	7.9	110	155	9 000	
4.2	7.4	920	110	5 040	
16.2	7.8	69	110	6 000	β-lactose 7–22.2
20.2	6.7	286	652	7 200	
22.2	8.0	45	413	9 000	
1.3	7.1	560	1 280	4 410	
B. A. 10 Months. Fig. 27					
1.2	8.1	103	127	3 800	
3.2	6.7	610	760	36 000	
15.2	6.3	610	740	27 000	β-lactose 7–24.2
20.2	6.5	60	740	22 000	
24.2	7.7	14	520	41 000	
28.2	7.4	220	500	34 200	
14.3	5.4	47	203	1 620	
A. K. 1 Year. Fig. 28					
30.1	6.6	630	580	20 770	
4.2	6.8	163	187	22 500	
13.2	7.0	560	650	29 000	β-lactose 7–14.2
14.2	6.2	414	302	35 000	
A. S. 7 Months Fig. 29					
1.2	7.7	3	3	< 100	
3.2	7.3	165	240	10 080	
14.2	6.0	90	560	66 000	β-lactose 7–15.2
15.2	6.3	21	34	9 000	

Table 32

Two Infants Fed on Mixed Diets without Lactose

Date	Faeces pH	Millions of Bacteria per 1 g of Faeces		
		Coliform	Growing on Dextrose Agar	Bact. Bifidum
F. H. 6 Months. Fig. 30				
16.1.50	8.1	1 800	1 700	45 000
31.1	5.9	620	740	2 250
7.2	4.5	133	96	8 000
1.3	6.8	1 060	6 600	6 000
B. L. 6 Months. Fig. 31				
20.12.49	7.4	290	—	< 1 000
7.1.50	8.1	220	590	21 000
13.1	7.7	70	50	1 440

Bibliography

ADAM, A.: Mschr Kinderhk *97:* 10—12: 500, 1949.
BERGEY, D.: Manual Determ. Bact. 1950.
BESSAU, G.: Mschr Kinderhk *68:* 297, 1937.
——: Dtsch Med. Wschr *64:* 12: 327, 1938.
——: Mschr Kinderhk *92:* 137, 1943.
BLAUROCK, G.: Mschr Kinderhk *68:* 304, 1937.
——: Zbl Bakt. I *144:* 75, 1939.
BOVENTER, K.: Zbl Bakt. I *142:* 17: 419, 1938.
BREIT, E.: Studien über die Darmflora des Menschen. Diss., Kiel, 1935.
DÜSTERWALD, W., KASTNER, W., and MÜLLER, H.: Med. Klin. *45:* 36: 1143, 1950.
EPSTEIN, B.: Acta Pædiatrica XVI: 521, 1933.
EPSTEIN, B. and JELINEK, O.: Arch Kinderhk *95:* 194, 1932.
GERSTLEY, J., PENRUDDOCKE, E., and LAURENCE, G.: Arch Pediatr. *52:* 552, 1935.
GERSTLEY, J., HOWELL, K., and ZABOROWSKI, H.: Ibid. *53:* 784, 1936.
HABILD, G.: Ztschr Kinderhk *67:* 206, 1949.
KLEINSCHMIDT, H.: Öst. Ztsch Kinderhk *3:* 55, 1949.
KRISTEN, G. and PETUELY, F.: Ibid. *4:* 121, 1950.
LEMBKE, A.: Arch Kinderhk *130:* 49, 1943.
LICHSTEIN, H.: J. Bact. *42:* 293, 1941.
MAASSEN, W. and ALBERTSEN, W.: Arch. Hyg. *123:* 367, 1940.
MALYOTH, G.: Klin. Wschr. *12:* 1930, 1933.
——: Ärztl. Wschr *5:* 13—14: 201, 1950.
MALYOTH, G. and KIRIMLIDIS, S.: Klin. Wschr *18:* 37: 1240 and 1270, 1939.
MALYOTH, G. and BAUER, A.: Ztschr Kinderhk *68:* 4: 358, 1950.
MALYOTH, G. and SPANIER, J.: Münch. Med. Wschr *92:* 15—16: 607, 1950.
MAYER, J.: Zschr Kinderk *65:* 293, 1947—48.
——: Mschr Kinderhk *97:* 9: 420, 1949.
——: Sixth Intern. Congr. Ped., Summaries of Communications p. 56, 1950.
MAYER, J. and MOSER, L.: Ztschr Kinderhk *67:* 455, 1950.
MORO, E., 1907—08: cit. Olsen, E., 1949.
MOSER, L.: Ztschr Kinderhk *68:* 25, 1950.
MÜLLER, E. and ROMINGER, E.: Kinderärztl. Praxis *16:* 7—8: 236, 1948.
OLSEN, E.: Studies on The Intestinal Flora of Infants. Diss., Copenhagen, Einar Munksgaard, 1949.
ORLA-JENSEN, S.: The Lactic Acid Bacteria. Kongel. Danske Vidensk. Selsk. biol. Skr. II: 3, 1943.
ORLA-JENSEN, S., OLSEN, E., and GEILL, T.: Ibid. III: 4, 1945.
PETUELY, F. and KRISTEN, G.: Ann. Pæd. *172:* 3: 183, 1949.
——: Sixth Intern. Congr. Ped., Summaries of Communications p. 56, 1950.
POLONOVSKI, M. and LESPAGNOL, A.: C. r Acad. Sci., Paris *192:* 1319, 1931.
PRIMNIG, A. and TURKUS, M.: Ztschr Kinderhk *63:* 595, 1943.
RITSCHEL, E.: Öst. Ztschr Kinderhk *1:* 299, 1948.
ROUFOGALIS, S.: Arch Gynäk. *171:* 459, 1941.
SAVELSBERG: cit. Adam, A., 1949.
SCHIMANSKY, M.: Ztschr Kinderhk *63:* 778, 1943.
SITTLER, P.: Cbl Bakt. I *47:* 14 and 145, 1908.
TISSIER, H.: Recherches sur la flore intestinale normale et pathologique du nourrisson, Paris, 1900.
WEISS, J. and RETTGER, L.[1]: J. Bact. *27:* 39, 1934.
——[2]: Ibid. *28:* 501, 1934.
WELCH, B.: Biometrika *29:* 350, 1938.

Fig. 39. Short and long uneven rods, the latter type slightly curved. Magnification 1 480 ×.

Fig. 40. Short rods, some of them bifurcated. Magnification 1 480 ×.

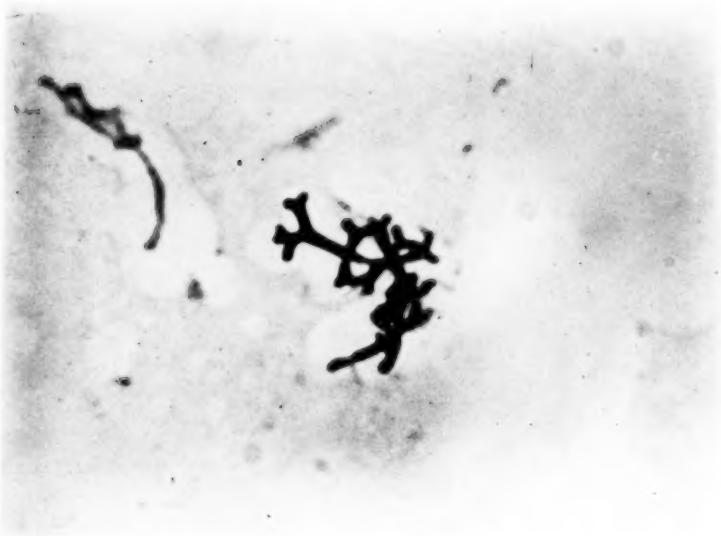


Fig. 41. Trifurcated rods. Magnification 2 200 ×.

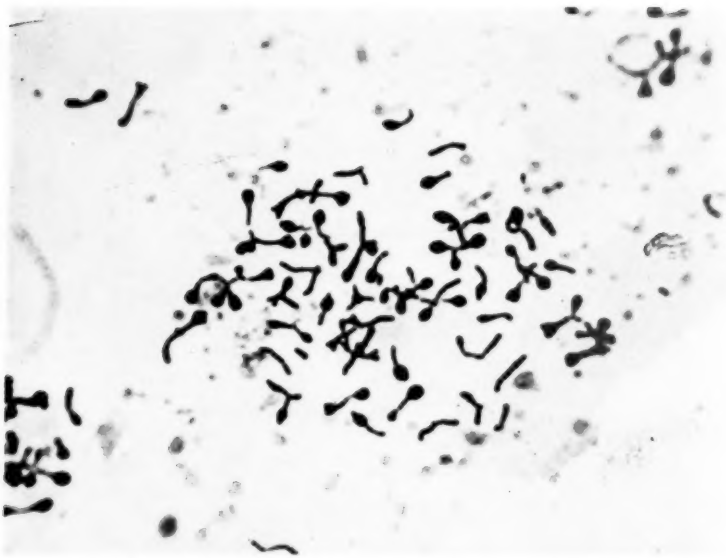


Fig. 42. Rods with globular or club-shaped extensions and branches. Magnification 1 320 ×.

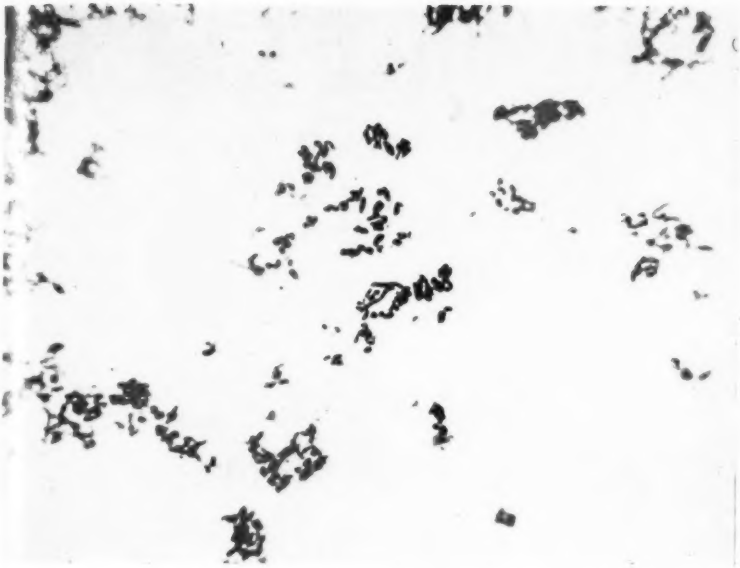


Fig. 43. Small coccus-like rods, including a few long, uneven S-shaped rods. Magnification 1 000 ×.

Fig. 44. Long, in part bifurcated rods with gram-negative stroma and gram-negative granules at the bifurcations etc. Magnification 1 480 ×.

All photomicrographs are of Gram-stained smears from bifidum colonies grown in tomato-peptone agar (ORLA-JENSEN) for three days at 37° C.

Acta Pædiatrica

Vol. 40 · May 1951 · Suppl. 81

UNIVERSITY
OF MICHIGAN
AUG 23 1951
MEDICAL
LIBRARY

ON THE WEIGHT AND STRUCTURE OF THE ADRENAL GLANDS AND THE FACTORS AFFECTING THEM, IN CHILDREN OF 0–2 YEARS

BY

HILKKA TÄHKÄ

HELSINGFORS, FINLAND

Almqvist & Wiksells Boktryckeri AB UPPSALA

List of Supplements to Acta Pædiatrica.

Vols. 1—40 (1923—1951).

1. **Muhl, Greta,** Über den Stoffwechsel des gesunden, natürlich ernährten Säuglings und dessen Beeinflussung durch Fettreduktion der Nahrung. Sw. Cr. 5: —.
2. **Höjer, J. Axel,** Studies in Scurvy. Sw. Cr. 5: —.
3. **Eriksson, Zaida,** Über Anstaltsschaden der Kinder: »Hospitalismus» in Kinderheimen. Sw. Cr. 3: —.
4. **Drucker, Paul,** Clinical Investigations into the Pathogenesis of Infantile Tetany. Sw. Cr. 3: —.
5. **Wallgren, Arvid,** Contribution à l'étude des splénomégalies de l'enfance. Sw. Cr. 5: —.
6. **Rhodin, Hans,** The Suspension-Stability of the Blood in Scarlatina. Sw. Cr. 3: —.
7. The Proceedings of the Fourth Scandinavian Pædiatric Congress, held at Helsingfors on June 28th—30th, 1927. Sw. Cr. 5: —.
8. **Herlitz, C. W.,** Studien über die Blutzuckerregulierung bei gesunden Säuglingen und solchen mit exsudativer Diathese. Sw. Cr. 3: —.
9. **Widnäs, Karin,** Études sur le diabète sucré chez l'enfant. Sw. Cr. 5: —.
10. **Gyllenswärd, Curt,** Some Sources of Error at Differential Count of White Corpuscles in Blood Stained Smears. Sw. Cr. 3: —.
11. **Salomonsen, Leif,** Periodisches Erbrechen und Ketonämie bei Kindern. Sw. Cr. 5: —.
12. **Wallgren, Arvid,** Erfahrungen über epidemischen Icterus (sog. Icterus catarrhalis). Sw. Cr. 5: —.
13. **Rietz, Einar,** Sterblichkeit und Todesursachen in den Kinderjahren. Sw. Cr. 5: —.
14. **Gyllenswärd, Curt,** Das weisse Blutbild bei Hunger und regelmässiger Nahrungszufuhr. Sw. Cr. 3: —.
15. **Skaar, T.,** Experimental Rickets. Sw. Cr. 5: —.
16. **Toverud, Kirsten Utheim,** and **Toverud, Guttorm,** Studies on the Mineral Metabolism during Pregnancy and Lactation and its Bearing on the Disposition to Rickets and Dental Caries. Sw. Cr. 5: —.
17. **Kloster, Johan,** The Distribution and Frequency of Rickets in one of the Fishery Districts of Finmark and Relation of Diet to the Disorder. Sw. Cr. 5: —.
18. **Svensgaard, Elisabeth,** Blood Sugar in Normal and Sick Children with Special Reference to Coeliac Disease. Sw. Cr. 5: —.
19. **Herlitz, C. W.,** A Contribution to the Knowledge of the Function of the Liver and the Reticulo-Endothelial System, Particularly in Infectious Diseases of Children. Sw. Cr. 3: —.
20. **Henschen, Folke,** Über Christians Syndrom und dessen Beziehungen zur allgemeinen Xanthomatose. Sw. Cr. 3: —.
21. **Bjørn-Hansen, Haakon,** Leukozyten-Untersuchungen bei den Masern. Sw. Cr. 5: —.
22. **Joukovsky, V. P.,** et **Rousskikh, V. N.,** Étude clinique et anatome-pathologique sur la tuberculose des centres nerveux chez l'enfant. Sw. Cr. 3: —.
23. **Huss, Ragnar,** Studien über die Schultz-Charltonsche Auslöschreaktion bei Scharlach. Sw. Cr. 5: —.
24. **Wickström, J.,** Eine elektrokardiographische Untersuchung über das Herz beim Scharlach. Sw. Cr. 3: —.
25. **Schiøtz, Carl,** Eine Darstellung und kritische Bewertung der Ursachen des Rückganges der Säuglingssterblichkeit in Norwegen. Sw. Cr. 5: —.
26. The Proceedings of the Sixth Northern Pediatric Congress, Stockholm August 27—August 29, 1934. Sw. Cr. 5: —.
27. **Rustung, Erling,** Studien über Rachitis. I. Mitteilung. Sw. Cr. 3: —.
28. **Sundal, Alfred,** Chronische infektiöse Erkrankungen der Harnwege im Kindesalter. Sw. Cr. 3: —.
29. **Magnusson, J. Henning,** Zur Kenntnis der Blutveränderungen bei Frühgeborenen. Sw. Cr. 5: —.
30. **Herlitz, C. W.,** Studien über den Krankheitsverlauf und die Therapie des Diabetes mellitus bei Kindern. **Söderling, B.,** Behandlung der Zuckerkrankheit im Kindesalter ohne Diäteinschränkungen. Sw. Cr. 5: —.
31. **Ström, Justus,** Periodisches Erbrechen mit Ketonämie bei Kindern. Sw. Cr. 5: —.
32. **Faxén, Nils,** The Red Blood Picture in Healthy Infants. Sw. Cr. 5: —.

FROM THE CHILDREN'S CLINIC OF THE UNIVERSITY OF HELSINKI, CHIEF: PROFESSOR ARVO YLPPÖ, M.D., AND FROM THE DEPARTMENT OF LEGAL MEDICINE OF THE UNIVERSITY OF HELSINKI, CHIEF: PROFESSOR UNTO UOTILA, M.D.

ON THE WEIGHT AND STRUCTURE OF THE ADRENAL GLANDS AND THE FACTORS AFFECTING THEM, IN CHILDREN OF 0–2 YEARS

By

HILKKA TÄHKÄ

Acta Pœdiatrica, Supplementum 81

Printed in Finland by
KESKUSKIRJAPAINO
Helsinki 1951

PREFACE

The present work was originally suggested to me in 1948 by my esteemed teacher, Professor ARVO YLPPÖ, M.D., Chief of the Children's Clinic. It gives me great pleasure to express my gratitude to him for providing me with the opportunity of carrying out scientific work at the Children's Clinic. The untiring interest shown by him in my work as well as his advice and encouragement have been of very great value to me.

I particularly wish to thank Professor UNTO UOTILA, M.D., Chief of the Department of Legal Medicine, who has not spared himself in guiding my work and on the basis of whose suggestions my work took its final form. Furthermore, I wish to express my gratitude for having been allowed to avail myself of the equipment of the Institute of which he is chief.

I am greatly indebted to E. K. AHVENAINEN, M.D., for the valuable advice I have received from him on patho-anatomic methods of research.

I wish to extend my best thanks to Professor C.-E. RÄIHÄ, M.D., for the valuable advice he has given and to NIILO HALLMAN, M.D., Assistant Chief of the Children's Clinic, for all the help I have recieved from him during my work.

My special thanks are due to Miss ULLA BAUER, who has carried out the majority of the stainings connected with my work.

I also wish to express my gratitude to all my colleagues and the nurses of the Children's Clinic, who have assisted me in many ways in the course of my work.

Finally I wish to thank KARI KARHUNEN, Ph. D. who has helped me with the statistical calculation of my material, and Mrs. HILKKA KONTIOPÄÄ, M.A., and Mr. L. A. KEYWORTH, M.A. (Cantab), for the translation of my work into English.

Financial assistance for the present work was granted to me by the Finnish Medical Society »Duodecim».

Helsinki, March 1951.

HILKKA TÄHKÄ.

CONTENTS

	Page
I. INTRODUCTION	7
II. THE PROBLEM	10
III. MATERIAL AND METHODS	11
Mathematical Review of the Results	14
IV. DEVELOPMENT OF THE WEIGHT OF THE ADRENAL GLANDS	16
Foetal Period	16
Postnatal Development of the Weight of the Adrenal Glands	17
Present Investigations:	
Fullterm Infants	20
Premature Births	21
Development of the Relative Weight of the Adrenals	22
Relationship of Birth Weight to the Weight of the Adrenals	24
Weight of the Adrenals in Female and Male Infants	25
Review of Results	26
V. FOETAL CORTEX	28
Present Investigations	30
VI. ON THE EFFECT OF DIFFERENT FACTORS ON THE ADRENALS	38
On the Effect of Diseases on the Adrenal Cortex	42
Present Investigations:	
Effect of the Duration of Disease on Adrenal Weight	43
Effect of the Duration of Disease on the Weight of the Adrenals in Different Diseases	45
Deviation Percentage of Adrenal Weight from So-Called Normal Weight as a Function of Duration of Disease	47
On the Influence of the Duration of Disease on the Relative Weight of the Adrenals	50
Results of Studies of the Effect of Duration of Disease on the Weight of the Adrenals	52
VII. ON THE LIPOIDS OF THE ADRENAL CORTEX	53
Lipoid Content of Adrenal Cortex in Different Diseases	53
On Qualitative and Quantitative Determinations of Adrenal Lipoids	55

Page

Present Investigations:
Comparison of Chemical and Staining Results 56
Lipoid Content in Different Disease Groups 58
Influence of Duration of Disease on Lipoid Content 58
Lipoid Content in the Different Layers of the Cortex 61
Premature and Newborn Infants 61
Miscellaneous and Diarrhoea Material 62
Results of the Present Investigations into Lipoids 62
VIII. THE ANDRENALS IN SOME PARTICULAR DISEASES 67
Cerebral Deformities 67
Congenital Heart Disease 68
Pyloric Stenosis 70
On Adrenal Haemorrhages 71
Patients who died of Pseudomonas Aeruginosa Septicaemia 72
Miscellaneous Cases 73
Results 74
IX. RELATIONSHIP OF THE ADRENALS TO THE THYMUS 76
X. RELATIONSHIP OF THE ADRENALS TO THE THYROID GLAND 79
Cases of Goitre 81
XI. DISCUSSION 83
XII. SUMMARY 88
XIII. REFERENCES 91

I. INTRODUCTION

EUSTACHIUS, in 1563, was the first to describe the adrenal glands with certainty, but not until the 18th century is there any evidence in the literature of attempts at elucidating their significance. In the middle of the 19th century adrenal research underwent a decisive change after ADDISON showed that the adrenals are indispensable to the maintenance of life, and described the disease bearing his name. The hundred years that have passed since then have seen an enormous number of investigations into the adrenals, with the purpose of studying their development, structure and function in different situations. By the early 20th century many investigators realised the great importance of the adrenals in the fight of the organism against various harmful factors, e.g. diseases. Basing their results on pathoanatomic findings, several investigators, e.g. THOMAS (1911), GOLDZIEHER (1910), LANDAU (1913), and others advance the opinion that death in acute infectious diseases is due, in the first place, to an insufficiency of adrenals.

The great susceptibility to infections of newborn infants and infants under 6 months has been explained by GOLDZIEHER (1946) as being due to a relative insufficiency of the adrenal cortex, which according to him is present in all children under 6 months. For a great part, he bases these assertions on the changes taking place at this age in the structure of the adrenals. This development of the adrenal cortex, the involution of the foetal cortex and formation of the permanent cortex, have been the subject of keen research. Several theories have been advanced on the significance of the foetal cortex and the factors affecting its involution (GOLDZIEHER 1946, HOWARD 1940, BLACKMAN 1946, etc.), but the problem still remains unsolved. Extensive evidence exists on the anatomic changes

visible in the course of this development (KERN 1911, BENNER 1940, SWINYARD 1943, BLACKMAN 1946, MCNEILL 1947).

Recent research has again accentuated the importance of the adrenal cortex. In 1946, SELYE, with his »General Adaptation Syndrome» theory, endeavoured to explain the reactions of the organism to most varied factors with the aid of a uniform mechanism, and one of the most important parts of this mechanism is the adrenal cortex. SELYE (1937, 1946) has shown with extensive animal tests that very varied factors, so-called stresses, produce fairly similar changes in the organism. The fate of the individual in each case is decided by the intensity and duration of the stress in question, and the organism's own resistance, or »adaptation energy». SELYE (1946, 1950), SAYERS & al. (1943—44) and numerous other investigators have found that this resistance of the organism is dependent, primarily, on the pituitary — adrenocortical system. It may depend on the reaction capacity of these organs whether the organism will be able to overcome the detrimental effects of the stress it suffers.

For instance, the above investigators have shown with extensive animal tests that both structural and functional changes are found, at the different stages of the activities of this defence mechanism of the organism, in several important organs, e.g. in the endocrine glands. A fairly great regularity can be shown, with animals, in the changes of the adrenal cortex. The changes e.g. in the size of the adrenal and its lipoid content are constant, to such an extent even that a characteristic finding permits far-reaching conclusions regarding the function of the adrenals.

Corresponding investigations, of course, cannot be carried out with man, but there are several points that justify the assumption that the pituitary — adrenocortical system, in the defence mechanism of the human organism too, has a leading function. This has emerged in connection with shock investigations for example (SELYE 1947. MOON 1942, LONG 1947, etc.).

It has been possible, at the convalescent stage of severe infectious diseases of long duration, to demonstrate relative insufficiency of the adrenal cortex (e.g. KAPPERT 1947, adults in and ROMINGER 1948, in children). It therefore seems possible that in cases where the disease was fatal, the infection was severe enough to result in so

considerable adrenal insufficiency that it must be considered as a principal reason for the exitus.

A new stage has again been reached in adrenal research in recent years, with the publication by HENCH, KENDALL & al. in 1949 of their discovery of and results with Cortisone and ACTH. The good results attained with these substances in a very varied range of morbid conditions clarify in a remarkable way the conception of the importance of the anterior lobe of the pituitary and the adrenal cortex in human organism.

The object of the present investigation has been to study the development of the adrenals from autopsy material, and the factors affecting them, and to try so ascertain whether conclusions can be drawn from autopsy findings as to the possible part played by the adrenal cortex in the death of infants.

It is possible to review the immensely extensive literature on the adrenals only in its main features in the following. Further information can be found in the detailed monographs by GOLDZIEHER (1946), HARTMAN & BROWNELL (1949) and SELYE (1950).

II. THE PROBLEM

On the basis of the material collected, the author endeavours to resolve the following problems:

1. The development of the absolute and relative weight of the adrenal glands in the course of the first two years of life and the effect of the birth-weight and sex of the infant on this development.

2. The involution of the foetal cortex and the effect on it of the infant's birth-weight, sex and diseases of varying kind and duration.

3. Changes in the weight of the adrenal glands in accordance with the duration of disease, and variations in such changes in the different diseases.

4. The varying of the lipoid content of the adrenal cortex with children of different ages and in diseases of varying kind and duration.

5. The existence of a law-like regularity in the relationship between the weights of the adrenal glands and the thymus.

6. The existence of a law-like regularity in the relationship between the weights of the adrenal glands and the thyroid gland.

7. The establishing of a possible insufficiency of the adrenal cortex, on the basis of investigations carried out, in some individuals or in certain groups of diseases.

8. The application of the results attained to the »General Adaptation Syndrome».

III. MATERIAL AND METHODS

The present material is collected from autopsies performed at Helsinki University Children's Clinic in 1948—1949. In addition, the author has had the opportunity of performing autopsies on some infants who died immediately after birth, made available by Helsinki University Women's Clinic.

The present material comprises 311 patients from whom the adrenal glands were removed; in 309 instances the thymus was also removed, and in 244 instances even the thyroid gland.

In the following the results are given for infants who died at 0—2 years of age, as the autopsy material of the Children's Clinic comprises so few older children that their grouping would have been practically impossible, and they have therefore been excluded.

Of the patients, 97 were premature and 214 fullterm births.

The breakdown of the present material by age and sex is as shown in Table 1.

Age	Premature births		Fullterm births	
	Male	Female	Male	Female
0— 7 days	19	29	19	9
8—14 »	7	5	5	7
15—30 »	4	3	13	4
1— 2 months	7	6	11	6
2— 3 »	4	3	18	11
3— 4 »	4	3	11	8
4— 5 »	1	1	13	9
5— 6 »	—	—	10	6
6— 9 »	1	—	15	11
9—12 »	—	—	7	5
12—24 »	—	—	6	10
Total	47	50	128	86

Table 1. The patients in the present material, by age and sex.

(The age grouping used in this table is consistent throughout the work. The age group 1—2 months, for instance, includes all the patients who died at the age of 31—60 days.)

By the main cause of death, the present material falls into the following groups (Table 2):

Cause of death	Number of instances
Premature birth	97
Debilitas congenita	2
Laesio cerebri intra partum	9
Vitia congenita cordis	15
Erythroblastosis foetalis	3
Icterus neonatorum gravis (not Rh)	4
Atresia oesophagi (operated)	4
Stenosis hypertrophicans pylori (operated)	2
» » » (not operated)	7
Septicaemia (Pseudomonas aeruginosa)	10
Other septicaemias	4
Meningitis purulenta	4
Pneumonia	27
Gastroenteritis	72
Lues congenita	1
Tuberculosis miliaris et meningeum	9
Encephalitis	2
Leucaemia	3
Diabetes mellitus	2
Idiotia mongoloidea	2
Anencephalus	1
Hydrocephalus (operated)	5
» (not operated)	2
Meningo- or encephalocele (operated)	4
» « » (not operated)	3
Status post laparatomiam	8
Malignant tumour	4
Miscellaneous	5
Total	311

Table 2. Material by diagnosis groups.

The above diagnoses and other relevant data were obtained from the case journals and post mortem records of the Children's Clinic. The author has tried, as a rule, to ascertain the principal disease of the infant and estimate e.g. the duration of the disease accordingly.

The autopsies were carried out within 1—48 hours of the patient's death, the majority within 12—24 hours. The adrenals, thymus and thyroid gland were removed by the author personally in all cases. The endeavour has been to prepare them as accurately as possible, removing the surrounding tissue. The fatty tissue surrounding the adrenal gland has often caused difficulties, as, sometimes, has the separation of a very atrophic thymus from the connective tissue.

Immediately on removal the organs were weighed, to an accuracy in 89 cases of 0.1 g and in 222 cases of 0.01 g. All the weighings were effected by the author personally, using the same weights and scale throughout, found on adjustment to weigh correctly to an accuracy of 1 mg.

After weighing the adrenal glands were cut into sections approx. 5 mm in thickness, which were fixed in 10 % formalin. 5 μ thick paraffin sections were then taken and stained with *Delafield's* haematoxylin and eosin. From these preparations, the amount of foetal cortex and permanent cortex was estimated by measuring in microscope the thickness of the entire cortex and foetal cortex at a total of 50 points on the sections taken from 4—5 different places in the adrenal glands . Mean values were calculated and the amount of foetal cortex was stated as a percentage of the entire cortex. A determination method of this type, naturally, is fairly uncertain, as a reliable result can only be obtained by volumetric determinations or calculations effected on serial sections. However, the results obtained can be considered indicative of the trend of development. The amount of medulla in the adrenal gland has not been measured as its amount in sections taken from different parts of the adrenal gland varies so much that no clear idea could be obtained using a method like the above. Details connected with the involution of the foetal cortex were observed and examination made for possible adrenal haemorrhages.

The lipoid content of the adrenal cortex has been considered as some kind of indicator of its function, as the active hormones of the adrenal gland are steroids (SELYE 1946, 1950, SAYERS & al. 1943—44, etc.). For the determination of lipoids and the so-called ketosteroids, several different methods have been used, e.g. Scarlet-red staining, Liebermann—Burchard—Schultze cholesterol staining, Feulgen's plasmal reaction, Bennett's phenylhydrazine staining, osmic acid staining; furthermore, the preparations were examined in polarized and ultraviolet light. Opinions in the literature on the value of the different determination methods are very contradictory (DEMPSEY & WISLOCKI 1946, DEANE & GREEP 1947, KNOUFF, BROWN & SCHNEIDER 1941, ROGERS & WILLIAMS 1947, DUGUID & MILLS 1928, BOSCOTT, MANDL, DANIELLI & SHOPPEE 1948).

Several 5 μ thick frozen sections were taken from all the adrenals in the material. *Scarlet-red* staining was used in every case. A further *Liebermann—Burchard—Schultze* cholesterol staining was carried out in 251 instances, and in 118 instances the sections were inspected unstained in *polarized light*.

The amount of lipoid content was estimated by eye and the following grading was employed:

0 = no lipoids
\+ = lipoid amount scarce
++ = » » fair
+++ = » » fairly abundant
++++ = » » abundant

Efforts have been made to judge the cases as uniformly as possible. In addition, the lipoid content of the different zones of the cortex was estimated separately in each case.

In 19 of the present cases, chemical lipoid analyses were made for other purposes (Hallman), and these results being available, it has been possible to compare the mutual relationship between the chemical and histological lipoid contents. The lipoid determinations were effected by the following methods:

Total lipoid: by BRUN's method (1939—40)

Cholesterols: by SCHOENHEIMER & SPERRY's method (1934).

Mathematical Review of the Results.

The following formulas have been employed in the calculations:

1. The symbols $x_1, x_2 \ldots x_k$ and $y_1 \ldots y_l$ denote the quantities measured. Hence,

$$\text{mean value of } x = m_1 = \frac{1}{k} \sum_{i=1}^{k} x_i,$$

$$\text{mean value of } y = m_2 = \frac{1}{l} \sum_{i=1}^{l} y_i,$$

$$\text{mean error of the mean value of } x = \sigma\,(m_1) =$$

$$= \sqrt{\frac{\sum_{k\,(k-1)}^{k} (x_1 - m_1)^2}{k\,(k-1)}} = \sqrt{\frac{\frac{1}{k}\sum^{k} x_1^2 - m_1^2}{k-1}}$$

The probability that m_1 deviates from the true value more than $2 \times \sigma\,(m)$ is 5 %, more than $2.6 \times \sigma\,(m)$ 1 %, and more than $3.3 \times \sigma\,(m)$ 0.1 %. It is assumed here that the quantities studied conform with the so-called normal distribution law, which assumption, in cases like the present, as a rule holds good with sufficient accuracy.

The mean error in the difference of two quantities, m_1 and m_2, is obtained from the formula

$$\sigma\,(m_1 - m_2) = \sqrt{\sigma\,(m_1)^2 + \sigma\,(m_2)^2}$$

2. The correlation coefficient between the quantities x and y has been computed from the formula

$$r = \frac{m_{12}}{\sqrt{m_{11} \cdot m_{12}}}$$

in which

$$m_{11} = \frac{1}{k}\sum_{i=1}^{k} x_i^2 - m_1^2,\quad m_{22} = \frac{1}{k}\sum_{i=1}^{k} y_i^2 - m^2{}_2,\quad m_{12} = \frac{1}{k}\sum_{i=1}^{1} x_i\, y_i - m_1\, m_2$$

Here, x_i and y_i, denote the corresponding x and y values, and m_1 and m_2 are the mean values of x and y.

To estimate the significance of the correlation, the quantity

$$t = \sqrt{k-2} \cdot \frac{r}{\sqrt{1-r^2}}$$

is employed.

The probability that the correlation found is significant can be obtained with the aid of t and k from the special table (so-called t-distribution).

3. The angle coefficient of the so-called regression line illustrating the rectilinear dependence of y on x is

$$b_{21} = r\sqrt{\frac{m_{22}}{m_{11}}}$$

In estimating whether b_{21} deviates from the given value β_{21} the following expression can be formed

$$t = \sqrt{\frac{m_{11}}{m_{22}} \cdot \frac{k-2}{1-r^2}}\ (b_{21} - \beta_{21})$$

upon which a study can be made, with the aid of the t-distribution table, of whether the value obtained differs significantly from zero.

If k is high, $t > 3.3$ corresponds to a 0.1 %, $t > 2.6$ to a 1 % and $t > 2$ to a 5 % probability of error in the conclusion that t deviates significantly from zero.

4. Denominations corresponding to agreed probability of error percentages, p, are often employed as follows:

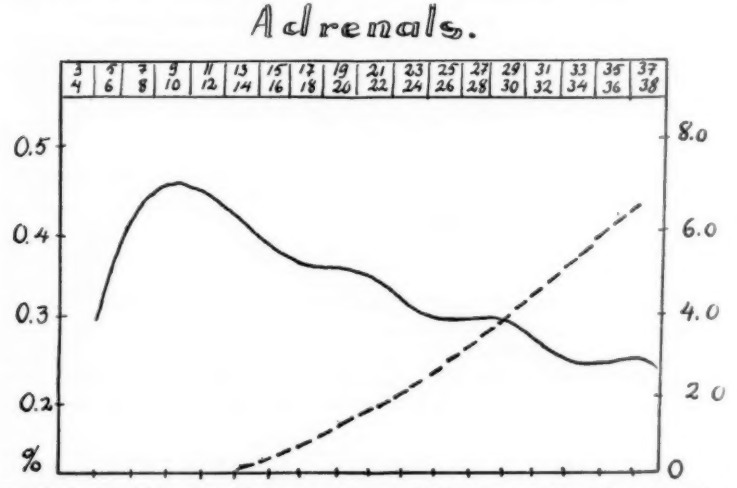
The difference observed is almost significant, if $1\ \% \leqq p < 5\ \%$
» » » » significant, if $0.1\ \% \leqq p < 1\ \%$
» » » » highly significant, if $p < 0.1\ \%$

The above formulas and the more detailed explanations connected with them are advanced e.g. by CRAMÉR 1949.

IV. DEVELOPMENT OF THE WEIGHT OF THE ADRENAL GLANDS

Foetal Period.

The development of the weight of the adrenal glands has been followed from the 3rd—4th months of pregnancy (JACKSON 1909, SCAMMON 1926, EKHOLM & NIEMINEVA 1950). In 1944 CLATWORTHY & ANDERSON published the normal foetal development of the weights of several organs. Their results are based on the values of JACKSON and SCAMMON, and on values collected by JACKSON from the literature. Graph 1 shows the development of the absolute and relative weight



Graph 1. Development of the absolute and relative weight of the adrenals in the foetal period, according to Clatworthy & Anderson.
– – – – – = absolute weight, g
——————— = relative weight, %

of the adrenals as given by CLATWORTHY & ANDERSON. The adrenal weights in foetuses of 75—2,500 g, published by EKHOLM & NIEMINEVA from Finland, coincide fairly well with the values given above. Among their results, the adrenal weights in foetuses from the immature stage (birthweight 600—1249 g) onwards are of particular interest in this connection. These values are given in Table 3.

Weight of foetus, g	Absolute weight of adrenal glands, g	Relative weight of adrenal glands	Number of instances
600—1249	2.4—3.7	1: 281 or 0.35 %	14
1250—2500	3.5—4.78	1: 94 or 0.25 %	16

Table 3. Adrenal weights, according to EKHOLM & NIEMINEVA, of foetuses of 600—2,500 g in weight.

According to BENNER, the weight of adrenal glands is proportionate to the length of the foetus. She gives the following mean values:

Length of foetus, cm	Weight of adrenals, g
25—30	3.8
31—35	3.3
36—40	4.0
41—45	5.7
46—50	6.4
51—55	10.3

SWINYARD has measured the volume of the adrenal glands with negroes, from a 3½-month foetus up to 17 years of age. He found that the adrenal cortex grows greatly towards the very end of pregnancy.

Postnatal Development of the Weight of the Adrenal Glands.

Table 4 gives the average weights of adrenal glands in fullterm newborn infants reported by the different researchers.

According to SCAMMON, the weight of the adrenal gland drops during the first two weeks of life by approx. 1/3 of the birth weight, and by about a half by the age of three months.

The following shows the average weights of the adrenal glands in various age groups as reported by certain researchers. The results are mean values from miscellaneous autopsic materials.

	Absolute weight of adrenal glands, g			Relative weight of adrenal glands, %		
		male	female		male	female
BENNER (1940)	6.4					
CASTALDI & VANNUCCI (1941)		9.01	7.19			
CLATWORTHY & ANDERSON (1944)	7.0			0.22		
ELLIOT & ARMOUR (1911)	4.6					
HASNER (1949)	4.9					
JACKSON (1909)				0.24		
SCAMMON (1926)	7—8					
SCHEEL (1908)	4.85	4.7	5.0			
SCHILF (1922)	6.83	7.37	6.39			
STARKEL & WEGRZYNOWSKI (1910)	6.2					
UOTILA (1940)		6.93	6.96		0.207	0.212

Table 4. Average weights of adrenal glands with fullterm newborn infants.

BENNER:

Age	Weight of the adrenal glands, g	Number of instances
Newborn	6.4	44
2 days	4—10	64
3 days—1 month	4—5	33
2—12 months	4—5	32
1—2 years	4.7	44

CASTALDI & VANNUCCI:

Age	Weight of the adrenal glands, g	
	male	female
8— 9 foetal months	3.44	3.45
newborn	9.01	7.19
0— 3 months	4.63	3.12
4— 6 »	3.43	2.29
7—12 »	4.34	3.74
1— 2 years	4.84	4.84

SCHILF:

Age	Weight of the adrenal glands, g	
	male	female
Premature infants	2.91	3.99
newborn	7.37	6.30
1 month	3.69	2.84
2 months	3.00	2.63
3 »	2.54	3.03
4 »	2.85	2 61
5 »	2.30	2.10
6 »	1.69	—
7—12 »	2.74	2.74
1 year	2.97	2.76
2 years	3.52	3.25

STARKEL & WEGRZYNOWSKI: 100 instances 0—5 years

Age	Weight of t adrenal glands,g
Stillbirths and premature births	6.2
0— 7 days	5.0
7 days—1 month	4.0
1— 2 months	3.0
2— 6 »	2.9
6—12 »	3.2
1—$1^1/_2$ years	3.1
$1^1/_2$—2 »	3.1
2— 3 »	4.9
3— 4 »	4.0
4— 5 »	6.0

HASNER:

Age	Weight of the adrenal glands, g
Newborn	4.9
6 months	2.8
12 »	3.1
2 years	3.3

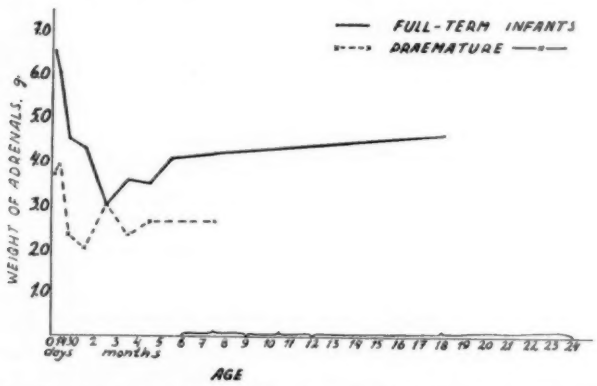
Age	Weight of adrenal glands, g		Number of instances	
	male	female	male	female
Newborn	6.9	7.0	88	76
0— 6 months.....	4.4	6.6	7	7
7—12 »	6.2	4.0	5	1
1 year	4.5	6.3	4	3

The weight of the adrenal glands of premature infants, given separately, has not been found in the literature. BENNER states, without specifying the instances, that the development of the weight of the adrenal glands of premature infants is similar to that of fullterm infants.

Present Investigations

Fullterm Infants.

Graph 2 shows the average weights of the adrenals for the fullterm infants of the present material, by the different age groups. Table 5 gives the same figures as accurate values.



Graph 2. Development of the adrenals according to age: fullterm infants and premature births.

Age	Weight of adrenals, g		Number of instances
	Mean value	Range	
0— 7 days	6.50±0.37	3.05—12.00	28
8—14 »	6.11±0.45	4.40— 9.85	13
15—30 »	4.52±0.31	2.00— 6.60	16
1— 2 months ...	4.30±0.36	1.63— 8.25	17
2— 3 » ...	3.51±0.22	1.71— 6.50	29
3— 4 » ...	4.10±0.28	2.50— 6.80	19
4— 5 » ...	4.03±0.30	2.30— 7.90	22
5— 6 » ...	4.64±0.27	2.58— 6.57	16
6— 9 » ...	4.69±0.24	2.78— 7.10	26
9—12 » ...	4.67±0.39	2.07— 7.12	12
12—24 » ...	5.23±0.39	3.54— 8.15	16

Table 5. Weight of the adrenals by the different age groups.

It can be seen from the above that there is scarely any change at all in the weight of the adrenals during the first 14 days. In the 15—30-day age group there was a distinct drop, from 6.50→4.52 g. The mean error in the difference between the mean values of the adrenal weights of the 0—7-day and 15—30-day age groups is ±0.48. The established reduction in weight is equal to 4.1 times the above mean error; hence the result is statistically highly significant. The average weight of the adrenals of infants of 15—30 days is 69 % of that of infants of 0—7 days.

Further it is seen that the adrenal weight drops continuously, attaining its lowest value, 3.51 g, at the age of 2—3 months. This figure is approx. 54 % of the adrenal weight of infants of 0—7 days. From the age of 3 months the weight of the adrenals begins to increase slowly, and the increase continues throughout the material; with infants of 12—24 months the average weight of the adrenals is 5.23 g i.e. still distinctly below the value at birth. Calcules of correlation show that the increase in the adrenal weight from the age of 3 months →24 months is highly significant.

Premature Births.

The development of adrenal weight with premature births is shown in Graph 2 and Table 6.

Age	Weight of the adrenals, g		Number of instances
	Average	Range	
0— 7 days	3.77±0.19	1.02—6.40	48
8—14 »	3.81±0.32	2.50—5.70	12
15—30 »	2.68±0.47	1.40—4.80	7
1— 2 months ...	2.00±0.14	1.60—2.90	13
2— 3 » ...	3.51±0.32	2.30—4.88	7
3— 4 » ...	2.75±0.35	1.63—4.00	7
4— 5 » ...	3.22	2.90—3.55	2
5— 6 » ...	—	— —	—
6— 9 » ...	3.07	— —	1

Table 6. Weight of the adrenals in the different age groups of premature births.

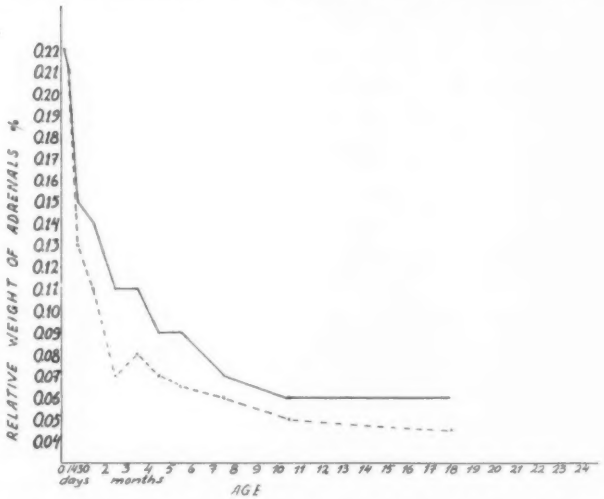
Graph 2 and Table 6 show that the weight of the adrenals, with premature births as well, remains practically constant up to the age of 14 days, upon which it begins to decrease. In the 15—30-days group the weight has fallen to 2.68, 71 % of the adrenal weight of the 0—7-day age group. The minimum value is already attained in the age group 1—2 months, when the adrenal weight is 2.00 g, or approx. 53 % of the initial value. In the following age groups the adrenal weight rises again, but no distinct law-like regularity can be discerned, the instances being too few in these older age groups.

Development of the Relative Weight of the Adrenals.

In observation of the development of the size of the different organs in the foetal period valuable help in judging the matter can be obtained from the relative weights of the organs in question, i.e. their weights compared with the body weight of the relevant foetus. The value of the relative weights is considerably reduced, in the postfoetal period, resulting from the fact that in the course of a disease an infant's nutritional condition, generally, deteriorates. Diseases of different kind and duration are very varying in effect in this respect. The relative values calculated from the established weight at death, therefore, are not comparable. To clarify the matter, a so-called ideal weight has been worked out for the patients of the material, employing

the generally accepted formula: birth weight + age in months × 600 g (SIMMONS & TODD 1938). The relative weights of the organs, also, in each individual case, have been calculated from this ideal weight. The values obtained in this way, admittedly, cannot be considered as normal results, as the ideal weights of the adrenals are not known.

Graph 3 shows the relative weight of the adrenals in fullterm infants, calculated from the established weight at death and from the estimated ideal weight. Both graphs have a distinctly declining

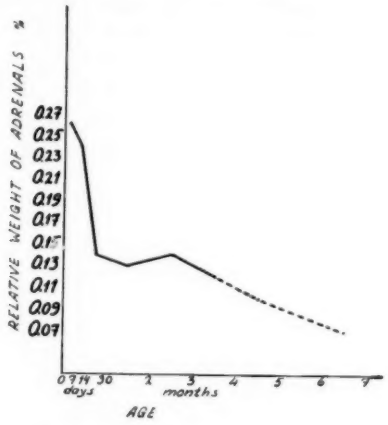


Graph 3. Development according to age of the relative weight of the adrenals: fullterm births.
———————— = calculated from the established weight at death
— — — — — — — — = calculated from the estimated ideal weight.

course, which in fact is natural, when the rapid growth of infants at this age is taken into consideration. Apart from the newborn infants (age at death under 15 days), the relative weights calculated from the ideal weight are distinctly lower than the values calculated from the weight at death.

Graph 4 shows the development of the relative weight of the adrenals in premature births. It has not been possible to work out

an ideal weight for this group as the development of the weight of premature births does not conform so distinctly to rule as does that of fullterm births.



Graph 4. Development of the relative weight of the adrenals with premature births.

A comparison of the graphs showing the relative weights of fullterm infants (calculated from the weight at death) and of premature births indicates that for premature babies the initial values are slightly higher than for fullterm births, but that from the 15—30-day age group onwards no distinct differences can be observed in the results.

Relationship of Birth Weight to the Weight of the Adrenals.

The fact that the adrenals have been found to grow considerably towards the very end of pregnancy (JACKSON 1909, SCAMMON, SWINYARD 1943, etc.), justifies a study of whether any correlation can be established in the present material between the birth weight of the infant and the adrenal weight ascertained. In Table 7 each group includes only infants who died within 24 hours of birth, thus excluding the influence of various external factors on the size of the adrenals.

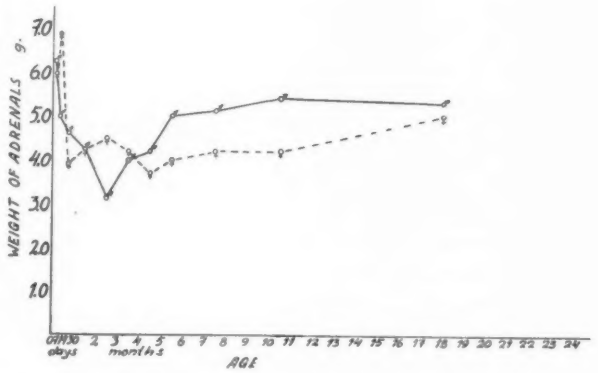
Birth weight, g	Average weight of adrenals		Number of instances
	Absolute g	Relative %	
800—1249	2.89±0.58	0.29	6
1250—1999	4.66±0.53	0.28	4
2000—2499	4.31±0.57	0.20	4
over 2500	6.23±0.48	0.23	4

Table 7. Relationship between birth weight and adrenal weight.

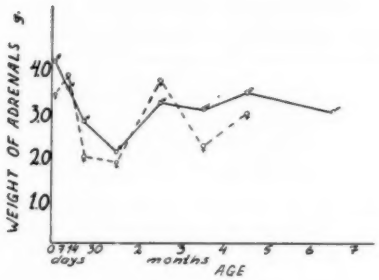
Although the instances are so few, it is obvious from Table 7, that the absolute weight of the adrenals increases considerably towards the end of the pregnancy, whereas the relative weight declines, probably due to the fact that the weight of the child, as is known, greatly increases in the last weeks of pregnancy.

Weight of the Adrenals in Female and Male Infants.

The average weights of the adrenals, separately for girls and boys, are shown, for fullterm births in Graph 5, and for premature births in Graph 6.



Graph 5. Development according to age of the weight of the adrenals in different sexes: fullterm births.



Graph 6. Development according to age of the weight of the adrenals in different sexes: premature births.

It can be concluded from these that no distint difference between the adrenal weights of the different sexes can be found. The differences in the older age groups of Graph 5 have no statistical significance.

Review of Results.

A review of the above results on the development of the weight of the adrenals shows that the trend of development coincides fairly well with the findings of other researchers (SCAMMON, SCHILF, STARKEL & WEGRZYNOWSKI). One difference, however, is that in the present material the average weight of the adrenals declines from 0→3 months and then starts to increase slowly, whereas in SCHILF's and in STARKEL & WEGRZYNOWSKI's material the decline in the weight of the adrenals continues up to 6 months. In addition, the absolute weights of the adrenals in the present material are somewhat higher than those found by the above researchers. These differences are probably due to difference in material, for the results of all the researchers are based on miscellaneous autopsic materials. SELYE (1937, 1946, 1950) and many others have shown that diseases and other stresses rapidly affect the size of the adrenals, and that the effect of stresses of different kinds and duration is varying. No normal material proper is available for comparison, accidental death being very rare at this age. — Another possibility to be considered is that in some cases the fairly great weight of the adrenals may be due to the fact that, in spite of attempts to

do so, it has been impossible entirely to remove the fat surrounding the adrenals.

The absolute weights of the adrenals are lower with premature births than with fullterm infants, but the trend of development is similar. With premature births, it is true, the postnatal reduction in size seems to be somewhat more rapid than with fullterm infants. The relative weights, on the other hand, are higher in premature births in the first two weeks of life, while no distinct difference can be shown later on.

The considerable growth of the adrenals towards the end of the pregnancy is also evident from this material, and the values obtained coincide fairly well with published results, e.g. CASTALDI & VANNUCCI, SCHILF, and EKHOLM & NIEMINEVA.

In CASTALDI & VANNUCCI's material the adrenals of female infants, generally, are somewhat smaller than those of male infants. The other researchers have not established this difference, nor has any difference between the sexes been found in the present material.

To summarise the results it can be said that:

1. With fullterm infants the absolute weight of the adrenals decreases up to the age of 3 months, representing at that point 54 % of the newborn value. The weight then begins to rise, and the rise continues throughout the material. At 2 years still the adrenal has not attained the weight at birth.

2. With premature births the adrenals decrease similarly but at a greater rate; the lowest value is found in the 1—2-month age group, representing approx. 53 % of the weight at birth.

3. The relative weight of the adrenals decreases throughout the material. Development is fairly identical with fullterm and premature births.

4. The adrenals grow considerably towards the end of pregnancy.

5. No difference is found in the adrenal weight of male and female infants.

V. FOETAL CORTEX.

The considerable decrease of the adrenals in the first few months of life is possibly due, to a great extent, to the involution of the so-called foetal cortex.

In the adrenal cortex of a newborn can be distinguished: a light-coloured, narrow exterior part and a large, sanguineous interior part. This observation was first published by STARKEL & WEGRZYNOWSKI (1910), and about simultaneuously by THOMAS (1911).

The light-coloured exterior layer is the so-called permanent cortex, and the dark interior part the so-called foetal cortex (HETT 1925, SWINYARD, BENNER etc.).

SWINYARD has measured separately the volumes of the permanent cortex and foetal cortex during and after the foetal period. He found that the considerable growth of the adrenals towards the termination of pregnancy is due to the immense growth of the foetal cortex at that time. According to SWINYARD, the foetal cortex constitutes approx. 85 % of the entire cortex of the newborn. HETT and KEENE & HEWER (1927) have assessed the amount of foetal cortex at approx. 65—75% of the entire cortex, and ELLIOT & ARMOUR at approx. 80 %.

Immediately after birth with the foetal cortex beginning to degenerate, considerable changes occur in the adrenal cortex (LANDAU, ELLIOTT & ARMOUR GOLDZIEHER 1946). KEENE & HEWER, however, maintain that the degeneration of the foetal cortex can be observed within the last ten weeks of pregnancy.

In 1911 the involution of the foetal cortex was described in detail for the first time by KERN. His work still constitutes the basis of subsequent research, and will be reviewed in the main below. KERN distinguishes four stages in the postfoetal development of the adrenal cortex:

I The stage of hyperaemia: From newborn to 1 month. The limits of the different parts of the cortex are still not quite distinguishable. Zona glomerulosa can be roughly distinguished from the interior part, which is hyperaemic, and in which some cellular degeneration is present.

II The stage of complete degeneration: Approx. 1—12 months. Zona glomerulosa, fasciculata and reticularis develop into the exterior part. The interior part displays hyperaemia, largedrop adiposis, phagocytosis, pigmentation, and increase of connective tissue.

III Medullary capsule formation: Approx. 1 year. The degenerated cells and hyperaemia disappear, and what remains is a thick capsule of connective tissue surrounding the medulla.

IV 1 year to puberty: The connective tissue capsule surrounding the medulla disappears, and the cortex and medulla grow contiguous.

GOLDZIEHER, BENNER, and MCNEILL have shown that the degeneration of the foetal cortex starts in its median parts, including the whole foetal cortex by the second week of life. According to MCNEILL, the foetal cortex proper has disappeared by the end of the third week. BENNER states that the connective tissue remaining from it begins to decrease rapidly at the age of 2 months, and with children of 5—6 months only a thin connective tissue capsule is found, which disappears at the age of 2—3 years. According to SWINYARD's volume measurements, this connective tissue capsule constitutes, in a child of 1 year, 15.9 % of the entire adrenal. In the course of the second year of life it gradually disappears.

The involution of the foetal cortex of premature babies takes place in the same way as that of fullterm babies (LEWIS & PAPPENHEIMER 1916, SWINYARD, BENNER).

At the same time as the foetal cortex is involuted a permanent cortex grows in its stead. According to Benner, the permanent cortex is doubled by the third week of life, and tripled by the end of the first month of life. From the third week onwards, zona glomerulosa and zona fasciculata can already be distinguished. Similar results have also been attained by KEENE & HEWER, SWINYARD, and MCNEILL. According to KEENE & HEWER, zona reticularis begins to develop at the age of

approx. 3 months. BLACKMAN, again, maintains that its beginning is already observable in the first postnatal week.

SWINYARD, BENNER, and BLACKMAN have shown that growth can be observed in the adrenal cortex throughout childhood up to puberty.

SWINYARD has also investigated the size of medulla by volumetric determinations. With the newborn there is little medulla, the ratio cortex: medulla being 214.7: 1. Medulla also grows throughout infancy, and at the age of 1 year the above ratio is 15.2: 1.

According to GOLDZIEHER (1946), the prenatal large foetal cortex is due to the relatively anoxemic condition of the foetus. This opinion is based e.g. on the finding that the involution of the foetal cortex is retarded in cyanotic children who have died of congenital heart malformations.

On the other hand BLACKMAN, HOWARD, etc. are of the opinion that the foetal cortex is androgenic in its function. This assumption is supported by the observation that a larger than normal foetal cortex has often been encountered in connection with the adrenogenital syndrome (DIJKHUIZEN & BEHR 1940, BLACKMAN, CARLGREN 1949, etc.).

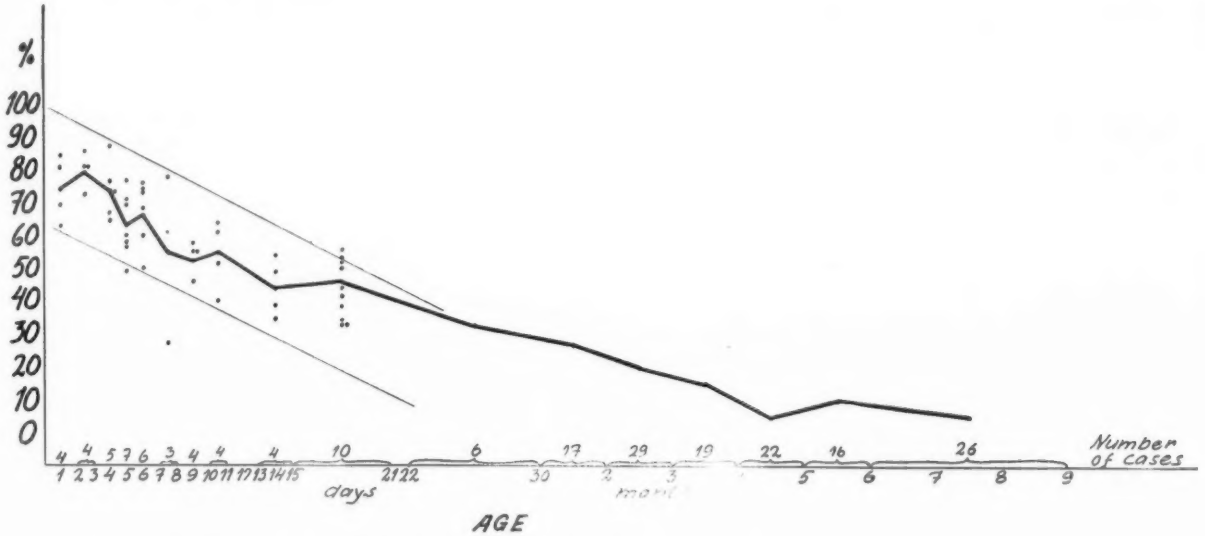
Furthermore, in some other diseases, changes have been found in the regular involution of the foetal cortex. These matters will be dealt with in greater detail later.

Present Investigations

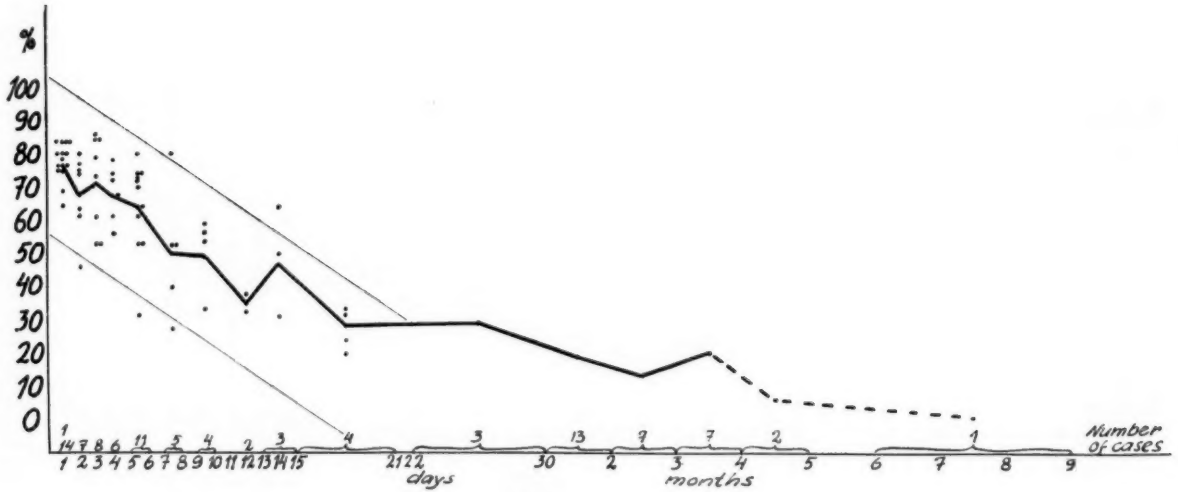
Graphs 7 and 8 show the development of the foetal cortex in fullterm and in premature babies. Up to the age of 21 days the mean value curve of the foetal cortex falls fairly evenly, although fluctuations in individual cases are considerable. Calcules of correlation show that no difference can be ascertained mathematically in the involution of the foetal cortex between fullterm and premature infants.

Table 8 shows that the development of the foetal cortex with premature infants in the different weight classes is identical; hence, the degree of prematurity does not affect the development.

The involution of the foetal cortex continues after 21 days of age, though less uniformly. At this age its histological picture begins to change distinctly. A distinct foetal cortex, with cells at different



Graph 7. Development of the foetal cortex with fullterm infants, indicates the normal range of variation to an accuracy of 1 %.



Graph 8. Development of the foetal cortex with premature births, indicates the normal range of variation, to an accuracy of 1 %.

Age	Birth weight 800—1249 g		Birth weight 1250—1999 g		Birth weight 2000—2499 g	
	Average foetal cortex %	Number of cases	Average f.c. %	Number of cases	Average f.c. %	Number of cases
1 day	79	6	78	4	75	4
2 days	73	3	54	2	74	2
3 »	69	2	74	6	—	—
4 »	—	—	68	5	67	1
5— 6 »	73	1	62	4	64	6
7— 8 »	—	—	51	5	—	—
9—10 »	—	—	57	2	43	2
11—12 »	—	—	33	1	37	1
13—14 »	—	—	47	2	50	1
15—21 »	31	1	28	2	20	1
22—30 »	—	—	28	1	29	2
1— 2 months	20	1	20	7	18	5
2— 3 »	—	—	13	3	15	4
3— 4 »	—	—	14	4	27	3
4— 5 »	—	—	6	1	8	1
5— 6 »	—	—	—	—	—	—
6— 9 »	—	—	0	1	—	—

Table 8. The development of foetal cortex in premature infants of various weights.

stages of degeneration and, in the majority of cases, hyperaemia and some connective tissue, has been found with all infants under 21 days.

From 21 days up to approx. 2—3 months a fair abundance of connective tissue, as a rule, is encountered as a residue of the foetal cortex, and in the connective tissue varying amounts of degenerating cells and hyperaemia. From the age of 3 months onwards, apart from a few exceptions, only a connective tissue capsule surrounding the medulla can usually be found. Already from 4 months onwards there have been some patients in which this connective tissue capsule has been so thin that it cannot be measured. Generally, the connective tissue capsule has been found in all children under one year and in the majority of the those older than 1 year.

According to GOLDZIEHER (1946), retardation of foetal cortex involution can be expected in connection with anoxia. Hence, a larger

than normal foetal cortex should be found in patients who have died of diseases in which respiratory difficulties and cyanosis were present. The most important among such diseases would be: premature birth, pneumonia, cerebral haemorrhages and congenital heart malformations. Graphs 7 and 8 and Table 8 show that premature birth as such has no effect. Tables 9 and 10 specify the cases in which the foetal cortex is considerably above the so-called normal range of variation, while Tables 11 and 12 show the instances in which the foetal cortex is smaller than normal. Tables 9 and 10 include no patients that died expressly of the above diseases. Nor can it be shown that the instances given in Tables 9 and 10 and in Tables 11 and 12 possess any essential differences as regards diagnosis, age, duration of disease or adrenal weight of the patients. Neither does the varying duration

Case No	Diagnosis	Age	Duration of disease	Weight of adrenals, g	Foetal cortex %	Average f.c. % at same age
254/48	Pneumonia	21 days	21 days	3.60	69	42
26/49	Icterus neonatorum gravis ...	21 »	21 »	4.98	56	42
256/48	Septicaemia	28 »	18 »	4.5	49	32
40/49	Haematoma subdurale	1½ months	1½ months	8.25	56	23
159/49	Vitium cordis cong.	1½ »	1½ »	3.99	50	23
369/48	Stenosis hypertr. pylori	2 »	2 »	4.3	34	18
94/49	Encephalocele ...	2 »	2 »	2.54	42	18
251/48	Tumor hepatis ...	2½ »	2 »	6.5	36	18
285/48	Gastroenteritis ...	3 »	1 »	4.0	32	15
407/48	»	3 »	1 »	6.00	35	15
224/49	Vitium cordis cong.	3 »	3 »	3.52	37	15
229/48	Gastroenteritis ...	3½ »	8 days	5.7	27	10
399/48	Vitium cordis cong.	4 »	4 months	3.32	30	8
409/48	Lues cong.	4 »	4 »	4.08	23	8
135/49	Pneumonia	5 »	8 days	6.57	20	6
362/48	Stenosis hypertr. pylori	5 »	4½ months	4.4	20	6
148/49	Gastroenteritis ...	6 »	4 days	6.35	20	5

Table 9. Fullterm infants in which the foetal cortex % is considerably higher than the average value.

Case No	Diagnosis	Age	Weight of adrenals, g	Foetal cortex %	Average foetal cortex % at same age
108/49	Præmaturus	8 days	5.62	80	55
3/49	»	14 »	3.14	64	32
239/48	»	1½ months	2.2	49	19

Table 10. Premature infants in which the foetal cortex % is considerably higher than the average value.

Case No	Diagnosis	Age	Duration of disease	Weight of adrenals	Foetal cortex %	Average f.c.% at same age
105/49	Septicaemia	5 days	1 day	4.98	48	63
415/48	Laesio cerebri intra part.	7 »	7 days	3.05	27	55
146/49	Vitium cordis cong	28 »	28 »	3.52	13	32
188/49	Meningomyelocele lumb.	1 month	1 month	3.22	12	26
57/49	Idiotia mongoloidea	2½ months	2½ months	1.78	5	19

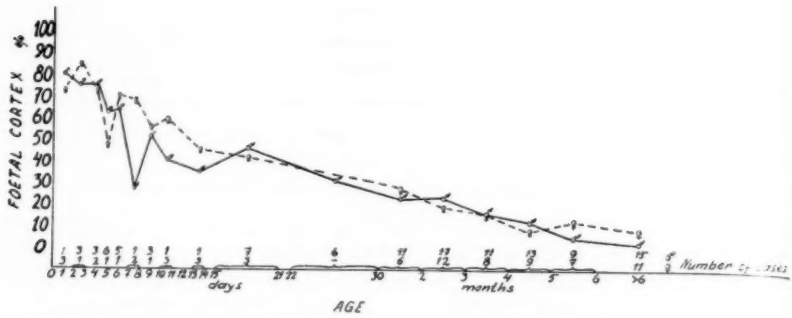
Table 11. Fullterm infants in which the foetal cortex % is considerably lower than the average value.

Case No	Diagnosis	Age	Weight of adrenals, g	Foetal cortex %	Average foetal cortex % at same age
92/49	Praematurus	2 days	3.88	45	75
144/49	»	6 »	5.82	32	63
102/49	»	8 »	4.75	27	55

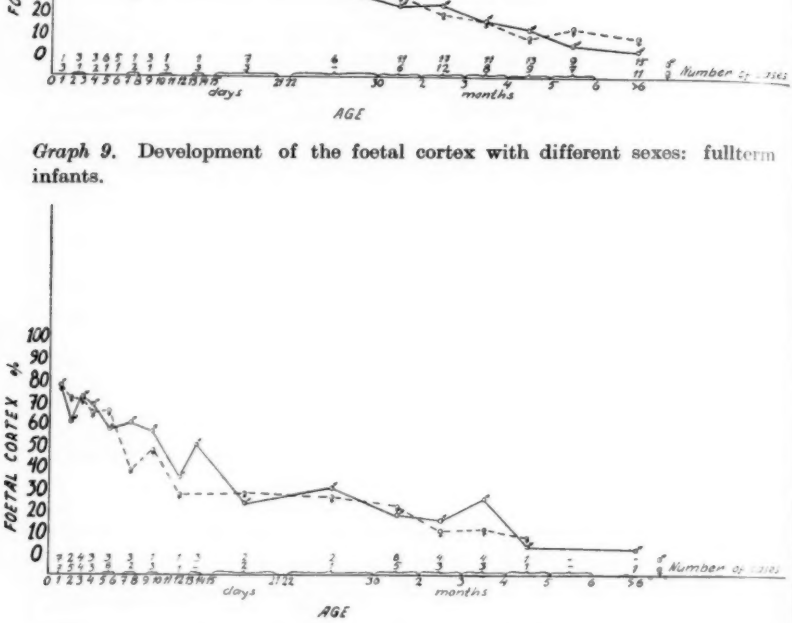
Table 12. Premature infants in which the foetal cortex % is considerably lower than the average value.

of the diseases affect the involution of the foetal adrenal cortex within the normal range of variation.

Graphs 9 and 10 show that no difference can be found between male and female infants in the development of the foetal cortex.



Graph 9. Development of the foetal cortex with different sexes: fullterm infants.



Graph 10. Development of the foetal cortex with different sexes: premature births.

Comparison of the involution of the foetal cortex with reduction in the adrenal weight in the first few motnhs of life shows that although the foetal cortex is considerably reduced within the first two weeks there is no change worth mentioning in the weight of the adrenals (Graph 2). The explanation is possibly that the development of the permanent cortex at this stage is capable of preventing the decrease of the organ, in spite of the degeneration of the foetal cortex. Later on.

with the more complete involution of the foetal cortex, the newformed permanent cortex can no longer prevent a reduction in the weight of the organ. The histological changes found with the patients of the present material at the different stages of the involution of the adrenal foetal cortex are very similar to those described by other researchers (KERN, BENNER, MCNEILL, etc.).

The attention is attracted particularly by the fact that the development of the size of the foetal cortex, and of the adrenal, is similar with fullterm and premature births, although it has been shown that it is towards the end of pregnancy that the adrenal and especially its foetal cortex grow considerably. It would therefore seem that the transition from intrauterine to the extrauterine condition has a decisive effect on the development of the adrenal cortex. This effect even seems to be independent of the degree of prematurity (Table 8). This phenomenon could be explained as being due to hormonal factors, e.g. the exclusion of the effect of the mother's hormones, in this case primarily ACTH, after birth.

In addition, it appears that the development of the foetal cortex is not dependent to any great degree on the various diseases of the infants, but does seem to bear correlation to their age. — Regarding the theory of the androgenic nature of the foetal cortex of the adrenal, no conclusion can be drawn on the basis of the investigations carried out.

To summarise the development of the foetal cortex, it can be said that:

1. The foetal cortex decreases fairly rectilinearly up to the age of 21 days, although individual variations may be considerable. Its decrease continues subsequently, but is no longer as regular.

2. Development with fullterm and premature infants is similar.

3. Histological changes present in the foetal cortex: to start with, degenerating cells, hyperaemia, later increased connective tissue content, and, from approx. 2—3 months to 1—2 years, a layer of connective tissue surrounding the medulla is found.

4. The kind and duration of disease suffered by the patients does not seem to affect the development of the foetal cortex.

5. The development of the foetal cortex is identical with male and female infants.

VI. ON THE EFFECT OF DIFFERENT FACTORS ON THE ADRENALS

SELYE (1946, 1950) has shown that the adrenal cortex reacts very readily to all kinds of stimuli. This is manifested in functional variations of the cortex, and is also reflected in the size and lipoid content of the adrenals. Changes in the size and lipoid content of the adrenals usually enter at the same time, and hence it may be advisable to deal with these points together. The adrenal findings caused by different stimuli are varying, being decisively affected in each case by the type of the stimulus in question, its intensity and duration, and the organism's own reaction capacity (SELYE 1946, SAYERS & SAYERS 1948, etc.). This explains why the results published in the literature differ and are often contradictory. Certain examples are given in the following.

SCHILF has found that the average adrenal weight with soldiers was 14.0 g, and with other adult males 11.7 g. He considers this due to the soldiers having been exposed to continued strain. A similar explanation is offered by ROGERS & RICHTER (1948) for the fact that the same rat strain when wild has larger adrenals than when living in captivity.

In 1906 ELLIOT & TUCKET found in animal tests that the adrenal cortex contained plenty of lipoids while the animal was at rest; in connection with some stress they were reduced.

Several investigators explain the disappearance of lipoids by increased activity of the adrenal cortex, and the storage of lipoids while the organ is at rest (SELYE 1946, SAYERS & al. 1943—44. SAYERS & SAYERS 1948, DOSNE & DALTON 1941, etc.). FLEXNER & GROLLMAN (1939), again, maintain the contrary.

With low atmospheric pressure tests, ARMSTRONG & HEIM (1938), GOLDZIEHER (1946), HAILMAN (1944), DARROW & SARASON (1944), etc., found that anoxia causes adrenal hypertrophy and a reduction in lipoid content.

KARWICKA (1911), KOLMER (1918), and LEWIS & PAPPENHEIMER are of the opinion that nutritional condition in no way affects the size and structure of the adrenals.

On the other hand, JACKSON (1915) has shown with rats that acute hunger causes an increase in the absolute and relative weight of the adrenals, whereas in chronic hunger the absolute weight is reduced and the relative increased. ELLIOT & TUCKET and SARASON (1943) observed that with acute hunger large adrenals poor in lipoids were found in the test animals. MULINOS & POMERANTZ (1941) have found atrophy of the adrenals in chronic malnutrition. The same was found by SELYE (1950), keeping test animals on a diet poor in proteins. SAYERS (1950) has come to the same conclusion.

According to SELYE (1946, 1950), the defence mechanism of the organism reacts to the greatest variety of noxious factors in the same way, in accordance with the principles of the so-called »General Adaptation Syndrome» (GAS). During the first stage of the GAS, the alarm reaction, when the defence mechanism of the organism begins to function, the adrenals grow larger and poor in lipoids, especially cholesterol. In the second, the stage of resistance, the adrenals remain large but the lipoid content returns practically to normal. In the third, the stage of exhaustion, in which the defence mechanism of the organism is broken down, the adrenals are again large and poor in lipoids.

In animal tests, SELYE (1937, 1946) elicited the GAS e.g. by muscular strain, thermic stimuli, poisons, infections, etc. DOSNE & DALTON found similar adrenal changes in connection with exposure to cold, and DEANE & MCKIBBON (1946) and DEANE & SHAW (1947) in lack of pantothenic acid.

The above contradictory results of adrenal changes elicited by hunger are explained by SELYE (1950) with the aid of the GAS as follows: Acute hunger causes an alarm reaction when the adrenals are large and poor in lipoids. In chronic hunger, again, the animals are at the stage of resistance, and the adrenals are rich in lipoids. A greatly prolonged state of hunger causes complete exhaustion when

the adrenals are free of lipoids, and necroses and haemorrhages are often found. Similar results have been achieved by UEHLINGER (1948) with human material.

SELYE emphasises the importance of the adrenocorticotropic hormone of the anterior pituitary (ACTH) as the regulator of the adrenal functions. SAYERS & al. (1943—44), and SAYERS & SAYERS (1948), in extensive investigations, have followed the influence of ACTH and the different stresses on the size and lipoid content of the adrenals. The instances are divided into 6 different groups as follows:

»Type 1. *Sudden temporary period of stress.* In this situation there is a sudden temporary increased demand for cortical hormones resulting in a temporary increase in pituitary adrenocorticotrophic activity. The sudanophilic substance, the cholesterol and the ascorbic acid undergo rapid depletion, following by a return of these substances to normal concentration as the animal recovers. A small increase in the size of the adrenal occurs. Typical examples of this type of adrenal response are produced by an acute nonfatal hemorrhage, a short bout of muscular exercise, a single dose of very short acting drugs as epinephrine or histamine. The changes in the adrenal characterized as Type 1 can be reproduced by the injection of a single dose of ACTH.

Type 2. *A very gradual change in the internal or external environment.*

Here there is a very gradual increase in the demand for cortical hormone which results in an equally gradual increase in pituitary adrenocorticotrophic activity. The concentration of sudanophilic substance, cholesterol and ascorbic acid of the adrenals remain essentially unchanged. A gradual increase in size of the gland occurs and it is apparent that new secretory units can be constructed at a rate sufficient to meet the increasing demands. Typical examples of this type are produced by fasting, seasonal changes in temperature, and pregnancy.

Type 3. *An intense continuous stress ending in death.*

There is a very great and continuous demand for cortical hormone resulting in a maximum rate of elaboration of ACTH from the pituitary. The concentration of sudanophilic substance, cholesterol and ascorbic acid falls rapidly and remains at a very low level until the

time of death. The gland is laying down secretory units at a maximum rate, as evidenced by its marked hypertrophy. The amount of this hypertrophy is proportional to the time which elapses between the onset of the stress and death. Typical examples of this type of adrenal response are produced by lethal doses of toxins, infectious disease leading to a fatal outcome, and burn, hemorrhagic and traumatic shock.

Type 4. *Recovery from a period of severe stress or adaptation to stress.*

In this case the demand for cortical hormone is reduced following a period of stress and the pituitary returns to a low state of functional activity. During the period of stress the adrenal becomes enlarged and depleted of sudanophilic substance, cholesterol and ascorbic acid. Upon removal of the stress these metabolic constituents accumulate in a manufacturing plant which is overexpanded for the needs of the organism under optimal conditions of the environment. — The initial depletion of the cholesterol content of the gland represents the toxic phase of the response. The return to normal and subsequent increase of concentration above normal represent the recovery phase. This type of adrenal response also occurs when an animal adapts to a continous applied noxious stimulus. It is of interest to note that the phase of accumulation of cholesterol and ascorbic acid in a hypertrophied gland correspond to the period of increased crossed resistance, which follows stress.

Type 5. *Dysfunction of the pituitary attended by hypersecretion of ACTH.*

In this case the organism has no need for increased amounts of cortical hormone but due to some dysfunction of the pituitary the adrenal cortex is stimulated to increased secretory activity. The adrenal is maximally increased in size and continuously depleted of its sudanophilic substance, cholesterol and ascorbic acid. The clinical example of this is Cushing's disease. The picture can be reproduced in the laboratory by chronic adiministration of large doses of ACTH.

Type 6. *Dysfunction of the pituitary attended by hyposecretion of ACTH.*

In this case the adrenal cortex atrophies as a result of pituitary

hypofunction. The sudanophilic material, the cholesterol, and the ascorbic acid of adrenal become inert at a high concentration. They are nonresponsive to changes in the internal and external environment. A clinical example of this type is found in pan-hypopituitarism (Simmonds'disease). In the laboratory it is produced by hypophysectomy.»

On the Effect of Diseases on the Adrenal Cortex

The literature contains frequent mentions of adrenal changes present in connection with different diseases, of which the main features are reviewed in the following.

In the 1910's LÖSCHKE, WELTMANN, GOLDZIEHER, etc., advanced the view that death in connection with acute fever diseases, particularly toxic diseases, such as dysentery and diphtheria, was due to adrenal insufficiency. The fact that cellular degenerations, small haemorrhages, round cell infiltrates, etc., have often been found in the adrenals on obduction, has been considered as supporting this assumption (VIRCHOW 1857, OPPENHEIMER & LOEPER 1901, SCHEEL 1908, BABES 1908, THOMAS 1911, KELLNER 1933, MACLEAN 1937, RICH 1944, etc.). In addition, e.g. GOLDEN (1948), found signs of exhaustion in the adrenals of malaria patients. — SELYE (1946) advances the opinion that, with man, a stress of long duration (e.g. illness) can cause the development of Addison's disease.

According to some investigators, insufficiency of the adrenal cortex is often present in severe infantile gastroenteritis. MACLEAN, SULLIVAN & ZWEMER (1932), as well as Heni (1941), support this conception with the electrolytic changes found in the plasma of diarrhoeal patients. v. SZÁZS (1939, 1941), FORSELL (1947, 1948), and BARTA (1948), again, in support of this conception, give the clinical picture of the disease and the positive results from treatment with desoxycorticosterone acetate. On the other hand, it is true, DARROW (1946), and DARROW & al. (1949) consider the administration of desoxycorticosterone in these cases as clearly contraindicated. According to GOLDZIEHER (1946), the great hydrolability of infants is due to relative adrenal insufficiency, and this hydrolability again accounts for the rapidly developing condition of dehydration in connection with diarrhoea.

Furthermore, mention of adrenal changes in some diseases peculiar

to newborn and infants is also made in the literature. These questions will be dealt with in greater detail later.

Some data on the weights of the adrenals of adults who died of various diseases are given in the literature (MATERNA & JANUSCHKE 1927, ADAMS & BAXTER 1948, UOTILA & PEKKARINEN 1951), but no corresponding figures for infant material have been found.

Present Investigations

Effect of the Duration of Disease on Adrenal Weight.

SELYE (1946, 1950) and SAYERS & al. (1943—44) have shown that the size of the adrenals is decisively affected by the duration of the stress in question. It may be justifiable, therefore, to consider the effect of the duration of the disease on the weight of the adrenals in the present material.

It has sometimes been difficult to judge the duration of the disease, e.g. if the patient has had a chronic disease but his death has resulted from some acute infectious disease for instance. In such cases an attempt has been made to estimate the patient's principal disease on the basis of clinical records and obduction findings, and to compute the duration of the disease accordingly. Premature babies have been excluded from this material as with them, in most cases, the duration of the disease is equal to the age.

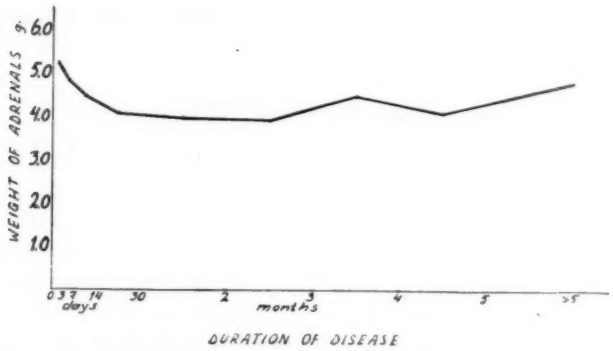
The material has been divided up into two groups; newborn, or those who died at the age of 0-14 days, and those who died at the age of 15 days to 2 years, since, as can be seen from Table 5, absolute adrenal weights at the age of 0-14 days are considerably higher than with the second group.

The adrenal weights of the newborn as a function of the duration of disease are given in Table 13.

Duration of disease	Weight of adrenals, g		Number of instances
	Average	Range	
0— 3 days	6.92±0.56	3.90—12.00	16
4— 7 »	6.16±0.49	3.05—11.10	14
8—14 »	5.94±0.41	4.40— 8.70	10

Table 13. Weight of adrenals as a function of the duration of disease with fullterm infants of 0—14 days.

Table 14 and Graph 11 show the absolute weights of the adrenals as a function of the duration of disease with children of 15 days to 2 years.



Graph 11. Development of the weight of the adrenals, according to the duration of disease: fullterm infants of 15 days to 2 years of age.

Duration of disease	Weight of adrenals, g		Number of instances
	Average	Range	
0— 3 days	5.19±0.32	3.08—7.90	17
4— 7 »	4.84±0.32	2.07—7.00	20
8—14 »	4.44±0.24	2.90—6.57	17
15—30 »	4.10±0.19	2.00—6.80	36
1— 2 months ...	3.94±0.24	1.63—8.25	35
2— 3 » ...	3.91±0.33	1.78—7.10	19
3— 4 » ...	4.48±0.50	2.50—8.15	9
4— 5 » ...	4.09±0.26	3.15—5.08	8
over 5 » ...	4.77±0.31	2.58—6.42	13

Table 14. Absolute weight of adrenals by the duration of disease with fullterm children of 15 days to 2 years.

The weight of the adrenals seems to be at its highest in patients who have died from diseases of the shortest duration (0—3 days). With extending duration of disease the average adrenal weight first drops, and from the 15—30-day duration of disease onwards there is little variation in the weight of the adrenals. An exception is constitut-

ed by the fairly high average adrenal weight found in the last group (duration of disease over 5 months). This may be due to the fact that the group includes a considerable number of patients suffering from e.g. congenital hydrocephalus or meningocele, who died of some acute infectious disease or from post-operative shock, and who could possibly have been placed in some other duration of disease group.

Effect of the Duration of Disease on the Weight of the Adrenals in Different Diseases.

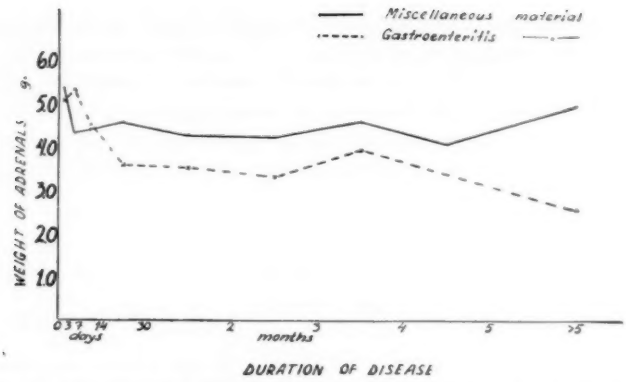
Table 2 shows that most of the disease groups are so small that the effect of the duration of disease on the weight of the adrenals cannot be demonstrated. An exception is constituted by the patients who died of gastroenteritis, totalling 72. In the following the intention is to study the development of the weight of the adrenals of patients who died of diarrhoea. The remaining material, termed »miscellaneous material», will be used as a comparison.

Table 15 and Graph 12 show the adrenal weights of diarrhoea patients as a function of the duration of disease.

Duration of disease	Weight of adrenals, g		Number of instances
	Average	Range	
0— 3 days	5.07±0.40	3.60—7.12	8
4— 7 »	5.30±0.34	3.80—7.00	10
8—14 »	4.49±0.28	3.20—5.70	9
15—30 »	3.64±0.20	2.32—5.40	18
1— 2 months ...	3.60±0.36	1.63—6.50	17
2— 3 » ...	3.35±0.20	2.30—3.99	7
3— 4 » ...	3.96	3.60—4.32	2
4— 5 » ...	—	— —	—
over 5 » ...	2.58	— —	1

Table 15. Weight of the adrenals as a function of the duration of disease: gastroenteritis material.

The corresponding figures for the miscellaneuous material are given in Table 16 and Graph 12.



Graph 12. Development of the weight of the adrenals according to the duration of disease: miscellaneous and diarrhoea materials.

Duration of disease	Weight of adrenals, g		Number of instances
	Average	Range	
0— 3 days.....	5.30±0.51	3.08—7.90	9
4— 7 »	4.38±0.51	2.07—6.60	10
8—14 »	4.49±0.40	2.90—6.57	8
15—30 »	4.55±0.29	2.00—6.80	18
1— 2months ...	4.27±0.32	2.90—8.25	18
2— 3 » ...	4.24±0.50	1.78—7.10	12
3— 4 » ...	4.64±0.72	2.50—8.15	7
4— 5 » ...	4.09±0.26	3.15—5.08	8
over 5 » ...	4.95±0.28	3.45—6.43	12

Table 16. Weight of the adrenals as a function of the duration of disease: miscellaneous material.

A comparison of the above tables and graphs shows that no difference worth mentioning is observable in the adrenal weights of patients dying syddenly (duration of disease 0—3 days) in the miscellaneous and the diarrhoea materials, whereas a distinct difference obtains in cases of lengthier duration of illness. The curve of the miscellaneous material, from the 4—7-days' duration group, remains fairly even, apart from a slight rise with durations exceeding 5 months. In the gastroenteritis material again, the curve shows a distinct fall from the duration group of 8—14 days onward, and the absolute

values are much lower than in the miscellaneous material. Calcules of correlation show that the decline in weight of the adrenals in diarrhoea patients is highly significant. The difference between the curves for the miscellaneous and the gastroenteritis materials is statistically significant.

Deviation Percentage of Adrenal Weight from the So-Called Normal Weight as a Function of Duration of Disease.

The variations in the absolute weight of the adrenals in accordance with the duration of the disease have been discussed above. The results are somewhat indefinite due to the fact that, as shown by Graph 2, the weight of the adrenals varies considerably in the different age groups, and that the breakdown of infants of different ages into groups of disease duration is completely haphazard.

To clarify the matter, a calculation has been effected in each case to show how much the adrenals deviate from the so-called normal weight for the age in question; the average values of these deviations have been calculated by groups of disease duration. There being no normal material proper available, it has been necessary to employ as »normal values» the average adrenal weights shown in Table 5. Although no true picture can be obtained with certainty in this way either, it is nevertheless of interest to compare the results thus obtained with those calculated from the absolute weights.

Duration of disease	Deviation from normal value %			Number of instances
	Average		Range	
0— 3 days.....	+ 7	+13±4.4	—22 — +50	8
4— 7 »	+19		— 9 — +75	10
8—14 »	+11		—20 — +54	9
15—30 »	— 9	—6±4.6	—41 — +50	18
1 —2months ...	— 3		—48 — +50	17
2— 3 » ...	—21	—21±4.0	—42 — —10	7
3— 4 » ...	— 9		—10 — — 8	2
4— 5 » ...	—		— —	—
over 5 » ...	—44		— —	1

Table 17. Gastroenteritis material. Deviations of adrenal weights as percentages of the so-called normal weight, by groups of disease duration.

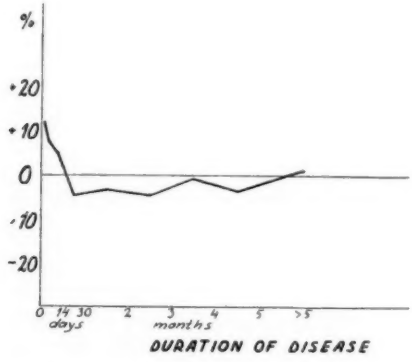
Duration of disease	Deviation from normal value %		Number of instances
	Average	Range	
0— 3 days.....	+17	—23 — +97	9
4— 7 »	— 3 +5±5.3	—47 — +47	10
8—14 »	± 0	—28 — +42	8
15—30 »	+ 1	—56 — +48	18
1— 2 months.....	— 4 —2±4.2	—34 — +87	18
2— 3 »	+ 6	—50 — +80	12
3— 4 »	+ 2	—39 — +57	7
4— 5 »	— 4 +3±4.6	—20 — +27	8
over 5 »	+ 4	—27 — +40	12

Table 18. Miscellaneous material. Deviations of adrenal weights as percentages of the so-called normal weight, by groups of disease duration.

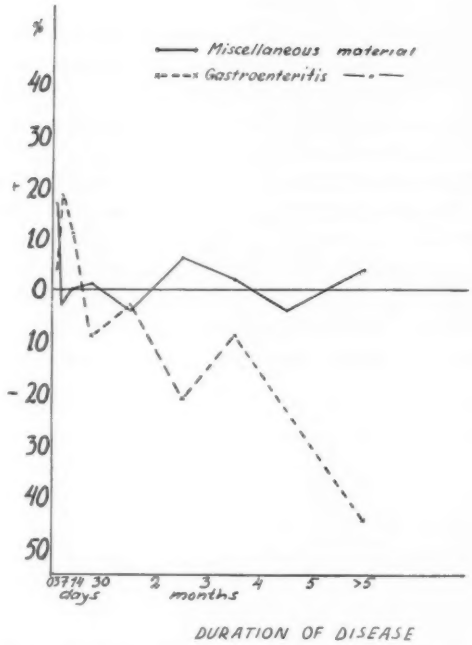
The following denominations have been used: normal value = 0, and the deviations are given as + or — percentages of this value.

Graphs 13 and 14 show the result in total. diarrhoea and miscellaneous materials.

Tables 17 and 18 give the results of the diarrhoea and miscellaneous materials specified in greater detail.



Graph 13. Adrenal weights as percentages of the so-called normal weight, grouped according to the duration of disease: fullterm infants of 15 days to 2 years of age.



Graph 14. Adrenal weights as percentages of the so-called normal weight, grouped according to the duration of disease: miscellaneous and diarrhoea materials.

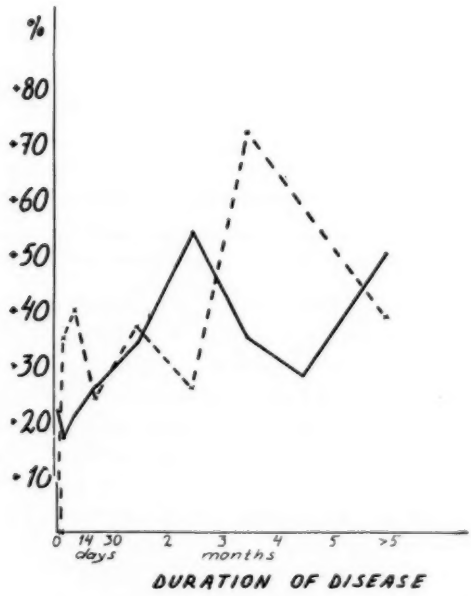
Comparison of the miscellaneous and diarrhoea materials thus obtained shows that up to a disease duration of 1—2 months no statistically demonstrable difference can be seen in the different groups. The mean value obtained for those with a disease exceeding 2 months in duration in the miscellaneous material is $+ 3 \pm 4.6$, and in the diarrhoea material $- 21 \pm 4.0$. The difference between these figures and the mean error of difference is $+ 24 \pm 6.1$, or the difference = approx. 4 times the mean error, which result is highly significant.

When considering Graph 14, the attention is also attracted by the fact that the miscellaneous material curve from the disease duration group of 4—7 days onward displays only slight deviations from the normal value, whereas the diarrhoea curve follows a declining course for disease durations of 14 days and over. It can be demonstrated that this decline of the diarrhoea curve is statistically significant.

On the Influence of the Duration of Disease on the Relative Weight of the Adrenals.

A review of variations in the relative weight of the adrenals connected with the duration of the disease must take into consideration the great dependence of this value on the age and nutritional condition of the child. Hence, the graphs illustrating this aspect of the problem have been worked out as follows.

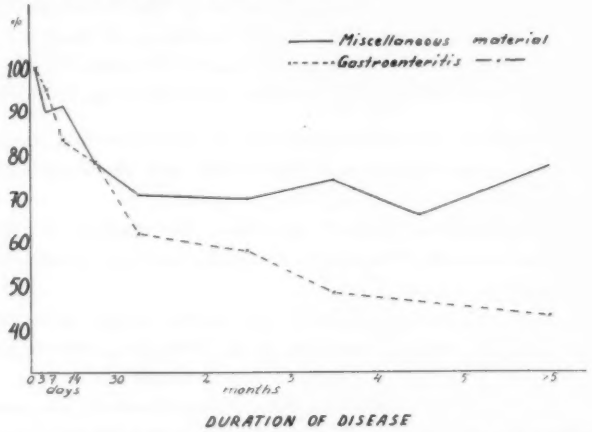
As »normal» have been considered the relative weights in the different age groups calculated from the ideal weights shown in Graph 3. In each case a calculation has been made to show how much the relative weight, computed from the weight at death, dif-



Graph 15. The relative weights of the adrenals as percentages of the so-called normal value, grouped according to the duration of disease: miscellaneous and diarrhoea materials. ———— = Miscellaneous material
— — — — = Gastroenteritis

fers from the »normal value». From results obtained in this way the mean values, given as + and — percentages, have been calculated by duration of disease groups.

Graph 15 shows the development of the relative weight calculated in this way for the miscellaneous and diarrhoea material. This should be studied in conjunction with Graph 16, which shows the loss in body weight calculated as a percentage of the ideal weight, grouped according to the duration of the disease.



Graph 16. Average loss in weight — as a percentage of the so-called ideal weight — as a function of the duration of disease: miscellaneous and diarrhoea materials.

Graph 15 shows that the relative weight is somewhat increased in the group of rapid deaths. In this group the weight at death does not differ from the ideal weight to any degree worth mentioning (Graph 16), and hence this increase in relative weights is not due to the drop in body weight. For patients with a lengthier duration of disease the relative weights vary a great deal in both graphs (+30—+70. The values are throughout considerably higher than the »normal» values. With these patients the weight at death, as a rule, has been distinctly below the ideal weight (Graph 16). This result indicates that the adrenals do not diminish in the same proportion as the patient loses weight. However the relative weight of the adrenals does not increase in the same proportion as the body weight is reduced, which

is obvious, as it was seen from the absolute weights that in chronic cases, particularly with diarrhoea patients, a reduction in the size of the adrenals can be observed.

Results of Studies of the Effect of Duration of Disease on the Weight of the Adrenals.

As no comprehensive infantile material on the development of the weight of the adrenals according to the duration of disease has been found in the literature, no comparison material exists for the results quoted above. To summarise the results obtained it can be stated that:

1. With patients who died of a disease of short duration, the absolute weight of the adrenals is distinctly higher than with those who died after a long disease.

2. With infants who died of diarrhoea, the absolute weight of the adrenals is continuously reduced after the initial increase, finally attaining subnormal values.

3. In the »miscellaneous» material, the absolute weight of the adrenals, after the initial rise, is fairly constant, in the first place perhaps »normal», from the 4—7-day disease duration group onwards.

4. The weights of the adrenals have been calculated as percentages of the »normal weights» of infants of the same age, and the results grouped according to the duration of disease. The results obtained in this way are similar to those calculated above from the absolute weights.

5. The relative weights of the adrenals have been dealt with according to the principle mentioned in item 4 above. The values obtained in this way are higher than normal throughout the material. However, the rise in relative weight suggested by the loss of body weight was not observed. This fact was evident with the diarrhoea patients particularly, for in cases of prolonged illness especially the weights of these patients have decreased a great deal.

VII. ON THE LIPOIDS OF THE ADRENAL CORTEX.

PLECKNICK (1902) has found lipoids as early as in the cortex of a 5 cm long foetus. At the moment of birth, according to KEENE & HEWER and STARKEL & WEGRZYNOWSKI, lipoids are present in the peripheral parts of the cortex only, whereas KAWAMURA (1911) has shown that sudanophilic lipoids are present in the peripheral parts only and birefringent lipoids throughout the cortex.

After the foetal period it is practically impossible to obtain any normal material on adrenal cortex lipoids for, according to SELYE (1946), diseases, traumata, etc., very readily affect the lipoid content of the adrenals.

ZWEMER (1936), BOURNE (1949), GOLDZIEHER (1946), etc., have given the following description of the lipoids of the adrenals in assumedly normal conditions of rest:

Zona glomerulosa: fair amount of small-granule fat formation.
Exterior part of fasciculata: plenty of large lipoid granules.
Interior » » » : less lipoids, and the granules are smaller.
Zona reticularis: a fair amount of small-granule lipoids.

According to the above investigators, the distribution of sudanophilic lipoids and birefringent substances are roughly equal.

Lipoid Content of Adrenal Cortex in Different Diseases

The lipoid content of the adrenal cortex in the various diseases has been studied a great deal, and the results are fairly varying. By way of general summary it can be said that, as a rule, adults who have died of acute diseases display fairly little, and those who have died of chronic diseases a fairly large amount of lipoids (LÖSCHKE 1910, KAWAMURA 1911, LANDAU 1913, GRAHAM 1916, PFEIFFER 1919, DEUCHER 1923, MATERNA & JANUSCHKE 1927, THADDEA 1938, LIEBEGOTT 1944, GOLDZIEHER 1946, VERZÁR 1948, ADAMS & BAXTER 1948, ROGERS & WILLIAMS 1949). WELTMANN (1913) has shown that

the hyperacutely dead generally have plenty of lipoids. According to him, the lipoid content varies considerably less with children than with adults. BORBERG (1915) states that the adrenals of children generally contain less lipoids than those of adults. The variations in the lipoid content of the adrenal cortex of infants suffering from different diseases have been studied e.g by TOBECK (1928), BLUMENSAAT (1929), ROSENBAUM (1931), and MENTEN & SMITH (1936). Each of them comes to the conclusion that, generally speaking, the adrenals of infants are relatively rich in lipoids, and that the most distinct loss of lipoids can be demonstrated in those who have died of chronic infectious diseases. All the materials, however, reveal very great individual variations. The lipoid content in the different zones of the adrenal cortex, according to the above-mentioned researchers, varies greatly with different diseases, but no distinct conformity to rule can be shown. MENTEN & SMITH have found that the stillborn and those who died at the age of a couple of days are very short of both sudanophilic and birefringent substances. Unfortunately, these researchers paid no detailed attention in their investigations to the effect of the duration of disease on the lipoid content, nor have they recorded the weights of the adrenals.

With infants who died of gastro-enteric intoxication KAWAMURA was unable to find any evidence of double refractive substances. The same result has been attained by BORBERG. WELTMANN again has found a fairly large amount of lipoids in the adrenals of diarrhoea patients who have suffered from a disease of lengthy duration.

HUEBSCHMANN (1921) and STEPHANI (1923) studied the lipoid content of the adrenals of infants who died of gastroenteritis. According to them, acute cases generally display low amounts of sudanophilic lipoids and birefringent substances; particularly marked is their absence from the zona glomerulosa. In chronic cases the results are varying. With three atrophic infants STEPHANI found adrenals rich in lipoids. — As control material he employed infants who had died of pneumonia, who generally had a fairly large amount of lipoids.

HALLMAN & AHVENAINEN (1950) have found great variations in the lipoid content of the adrenals in 47 infants who died of gastroenteritis. They have been unable to demonstrate any loss of lipoids from the zona glomerulosa.

Gastro-enteric patients usually display disturbances in mineral

metabolism, e.g. in the Na and K content of the organism (GAMBLE 1947, DARROW 1946, HALLMAN,). NICHOLS & HILL (1948) found in animal tests that, in the absence of Na and K, lipoids disappear from the exterior parts of the adrenals. DEANE, SHAW & GREEP (1948), similarly, have shown signs of increased activity in test animals in the zona glomerulosa (e.g. loss of lipoids) when there is a shortage of Na or of both Na and K. If the organism contains an excess of Na, lipoids accumulate in the area of the zona glomerulosa. With infants who had died of gastroenteritis, HALLMAN & TÄHKÄ (1950) were unable to establish any correlation between the Na and K content of serum and erythrocytes and the lipoid content of the zona glomerulosa.

On Qualitative and Quantitative Determinations of Adrenal Lipoids

The lipoid content of the adrenals has been widely investigated both chemically and histologically, and the results attained by the different investigators are even very contradictory.

FEX (1920) and HERMANN (1940) emphasise the inaccurary of histological methods of determination compared with the chemical, whereas KAY & WHITEHEAD (1935), KNOUFF & al. (1941), SAYERS & al. (1943—44), and ROGERS & WILLIAMS (1947) show that the results attained with these two methods are fairly well correlated.

The results of some investigators may be mentioned as examples of chemical lipoid determinations:

NEYMANN (1939) effected chemical determinations of the cholesterol content with foetuses of 6—9 months and gives the following average values:

free cholesterol	224	mg%	of	the	wet	weight	of	adrenals	
ester	»	298	»	»	»	»	»	»	»
total	»	522	»	»	»	»	»	»	»

With fullterm newborn the cholesterol content, according to BEUMER (1921), is 1340 mg%, and according to CHAUFFORD & al. (1914) 3600 mg% of the dry weight of the adrenals.

HERMANN and BEUMER have carried out chemical cholesterol determinations with infants and LAGE (1940) with children of 2—6 years of age. The total cholesterol content varies between 1000 and 5500 mg% of the dry weight of the adrenals. No regularity can be

observed in the proportion of free cholesterol and cholesterol ester. The lowest values were found with patients who had died of gastro-enteric intoxication.

Present Investigations

Comparison of Chemical and Staining Results.

Table 19 specifies the cases in which both chemical and histological lipoid investigation was carried out.

Case No	Age	Duration of disease	Diagnosis	Chemical [1] determinations			Histological [2] determinations		
				Total lipoids	Total chol.	Est. chol.	S—R	L—B—S	
79/49	1 day	1 day	Praematurus	9.31	1.90		+	++	
92/49	2 days	2 days	»	23.87	1.75		+	+	
91/49	3 »	3 »	»	31.59	9.08		++	+++	
93/49	3 »	3 »	»	28.29	3.67		+	+	
78/49	25 »	25 »	»	11.66	7.25		+	+++	
172/49	22 »	10 »	Gastro-enteritis	51.53	9.91	7.12	++	+++	+
231/49	2 months	13 »		47.44	3.72	1.55	++	+	+
227/49	2½ »	19 »	»	32.55	3.82	2.34	+	+	+
261/49	3 »	30 »	»	61.72	10.53	7.88	++++	+++	+
171/49	3½ »	20 »	»	45.00	4.59	2.68	++	++	+
259/49	3½ »	18 »	»	32.61	4.28	2.65	+	++	+
222/49	5 »	21 »	»	52.74	2.63	1.86	++	+	+
42/49	5½ »	2 »	»	71.28	0.93	0.30	++	0	
184/49	6 »	21 »	»	81.98	16.05	13.51	++++	+++	+
48/49	9 »	1 »	»	33.27	1.18	0.84	++	0	
247/49	10 »	3 »	»	34.95	4.24	2.93	++	++	+
83/49	15 days	5 »	Pneumonia	31.20	3.84	2.07	++	+++	
43/49	2 months	1½ months	Stenosis pylori	26.50	3.70	3.08	+	++	
63/49	9½ »	5 days	Status post laparatomiam	52.36	1.24	1.06	+	0	

[1]) Results as percentages of the dry weight of adrenals
[2]) S—R = Scarlet-red staining
L—B—S = Liebermann—Burchard—Schultze staining
Pol = result with polarized light.

Table 19. Chemical and histological determination of lipoids.

The results show that the lipoid content varies considerably in the different cases. In addition, it is noted that the total lipoid and cholesterol contents do not always follow the same course, as is seen e.g. from Cases 42/49 and 78/49.

The extent to which the lipoid contents estimated from the chemical and histological preparations in the present material are correlated in the material, is seen from Table 20.

Lipoid content		Number of cases
Histological determination	Mean value of chemical determinations	
Scarlet-red staining	Total lipoid content %	
0	—	0
+	27.1	8
++	46.3	9
+++	—	0
++++	71.3	2
Liebermann—Burchard—Schultze staining	Total cholesterol content %	
0	1.12	3
+	2.91	6
++	4.20	4
+++	7.89	4
++++	13.56	2
Double refracting substances	Total cholesterol content %	
0	—	0
+	3.81	5
++	7.07	2
+++	10.53	1
++++	16.05	1

Table 20. Relationship of chemical and histological lipoid determinations.

According to Table 19, the results obtained by chemical and histological methods of determination do not correspond in all individual cases. However, as can be seen from Table 20, the mean value results with the different staining methods are fairly similar. Unfortunately, the material is so small that the matter cannot be proved mathematically.

Lipoid Content in Different Disease Groups.

Fig. 1 shows the percentage distribution of the lipoid content ascertained by the different staining methods in the miscellaneous and diarrhoea materials, and with premature infants and fullterm newborn of 0—14 days of age.

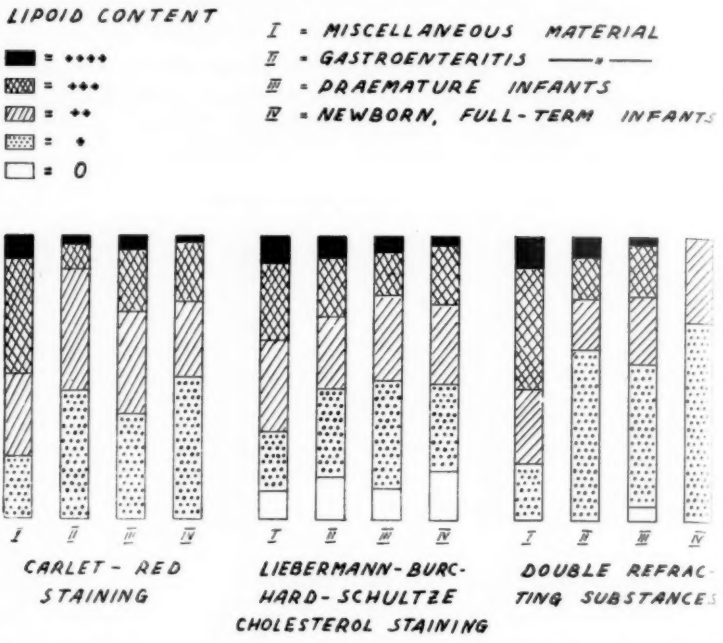


Fig. 1. Lipoid content in the different disease groups and by the different staining methods.

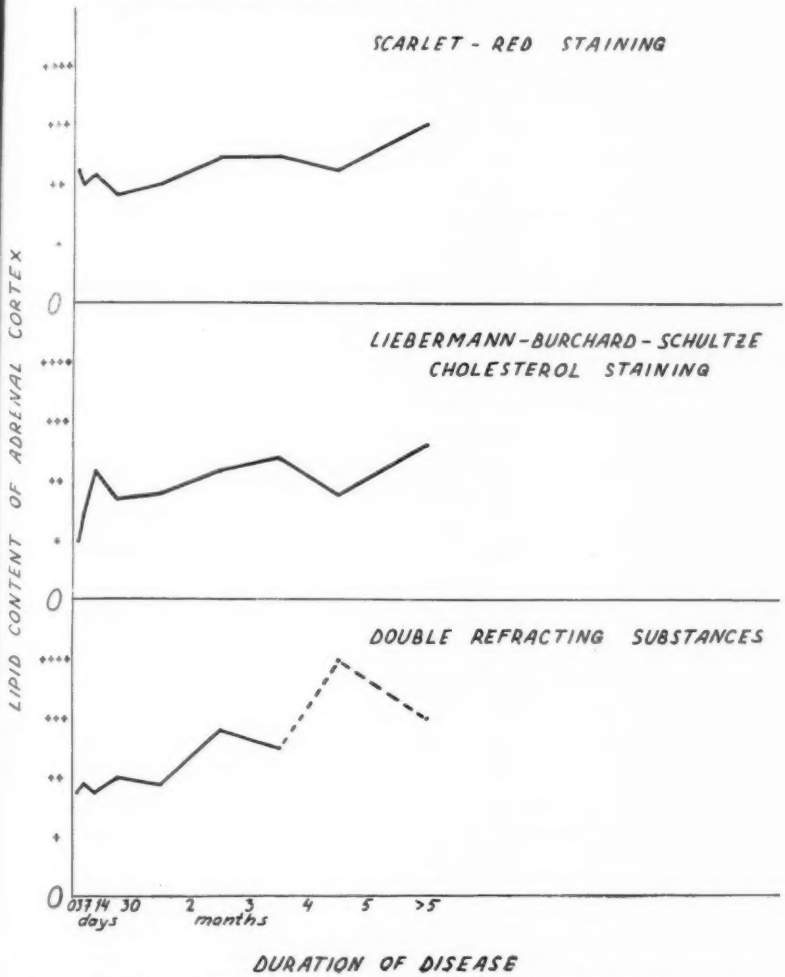
The columns show that the only difference fairly distinctly discernible in all the different staining methods is that the lipoid content in the miscellaneous material cases, on the average, is somewhat higher than in the other groups.

Influence of Duration of Disease on Lipoid Content.

In order to make the material conform in this respect to the weight materials above, principal attention has been paid to fullterm infants

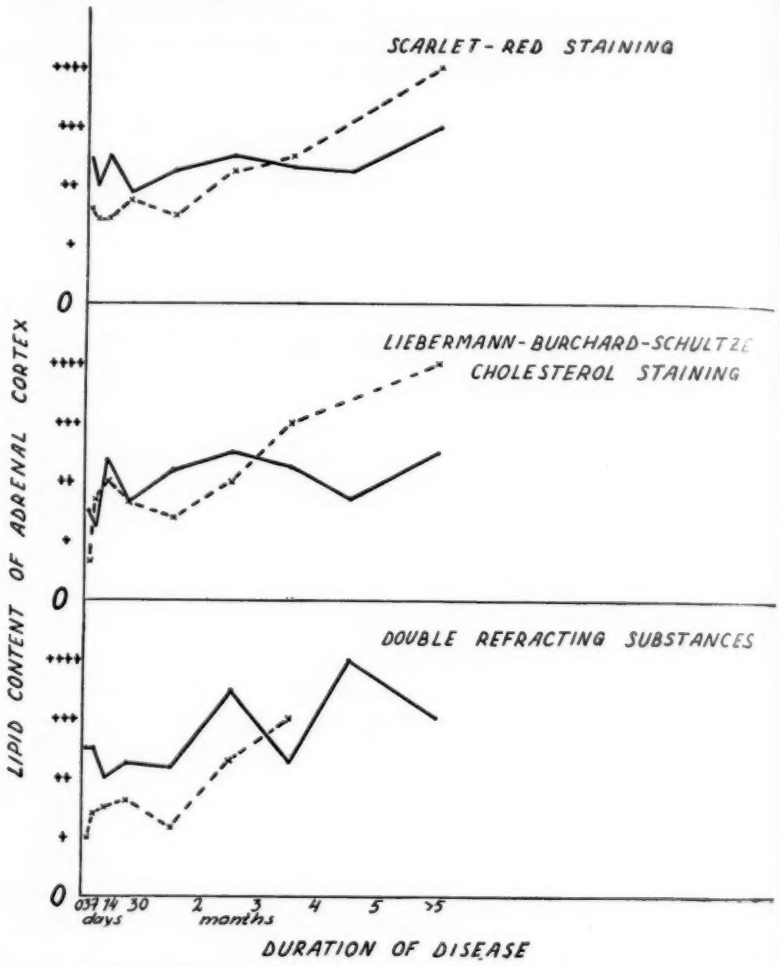
of 15 days to 2 years. The variations in the lipoid content of the total material and of the miscellaneous and diarrhoea cases have been dealt with separately.

Average lipoid content, as a function of the duration of disease, in the total material, is shown by Graph 17.



Graph 17. Lipoid content as a function of the duration of disease: fullterm infants of 15 days to 2 years of age.

The same is shown for miscellaneous material and diarrhoea material in Graph 18.



Graph 18. Lipoid content as a function of the duration of disease: miscellaneous and diarrhoea materials.

———————— = miscellaneous material

— — — — — — — — = diarrhoea material

The graphs show that the tendency in all materials seems to be that those dying from acute diseases, on an average, have less lipoids than those who died of a disease of lengthy duration. Calcules of correlation show that the rise of the cholesterol staining curve in the diarrhoea material is significant. In the miscellaneous material, again, the rise of the curve cannot be proved to be statistically reliable. The dissimilarity between the curves of the diarrhoea and miscellaneous materials is statistically almost significant.

With newborn (0—14 days) no distinct differences due to the duration of the disease can be shown in the lipoid content.

Lipoid Content in the Different Layers of the Cortex. Premature and Newborn Infants.

Table 21 shows the variations in the lipoid content of the different layers of the adrenal cortex of premature infants. In these cases it is often impossible to divide the permanent cortex into different zones with any certainty, for which reason the terms »exterior and interior part of the permanent cortex» will be used. The table has been computed from cholesterol staining results.

Table 22 shows the same for fullterm newborn.

On the basis of Table 21 it can be said that the lipoid content is somewhat lower with premature infants in the young age groups than in the older groups. As with premature infants generally age = duration of disease, this phenomenon is fully compatible with the observation that the adrenals of persons who have died of chronic diseases are as a rule rich in lipoids.

Both tables (21 and 22) reveal that complete loss of lipoids is somewhat more frequent in the area of the permanent cortex than that of the foetal cortex. However, individual variations are so considerable and the materials in the different age groups of such varying extent that no distinct law-like regularity can be established on the basis of the present material.

Miscellaneous and Diarrhoea Material.

As Graphs 17 and 18 show, the lipoid content of the adrenals varies considerably according to the duration of the disease. Hence, the lipoid contents in the different cortical layers of patients in the miscellaneous and gastroenteritis material are given divided up into groups according to the duration of disease. Table 23 shows these results in the miscellaneous material and Table 24 gives the same data on the gastroenteritis material.

A study of tables 23 and 24 shows that no distinct regularity is ascertainable in the variation in lipoid content of the different layers of the adrenal cortex. The results do not corroborate Stephani's finding, that loss of lipoids in the zona glomerulosa is strikingly frequent withdiarrhoea patients.

Results of the present Investigations into Lipoids.

The records found in the literature regarding the variations in the lipoid content of the adrenals in patients who have died of different diseases, are often very contradictory. This may be due, in the first place, to dissimilarity of materials and possibly also to some extent to the different methods of determining the lipoid content. Taking this into consideration, there is little point in comparing the results obtained in the present investigation with the results published by other investigators.

To summarise the results obtained it can be stated that:

1. Lipoid determinations by chemical and histological methods are fairly well correlated. The results with the three histological methods of determination employed are fairly similar, though there are exceptions in individual cases.

2. The average lipoid content given by all methods is greater in the miscellaneous material than in the diarrhoea, premature or newborn infant materials.

3. In the total material the lipoid content in cases of acute disease is smaller than in those with a disease of long duration. This is only

Age	Permanent cortex										Foetal cortex					Total number of cases
	Exterior part					Interior part										
	0	+	++	+++	++++	0	+	++	+++	++++	0	+	++	+++	++++	
0— 7 days	15	20	7	—	1	19	13	9	1	1	10	15	16	2	—	43
8—14 »	4	5	2	1	—	3	3	5	1	—	2	2	2	6	—	12
15—30 »	2	2	1	—	1	1	3	1	—	1	1	2	0	3	—	6
1—2 months	2	3	3	1	1	2	1	2	4	1	1	1	3	3	2	10
2—3 »	—	3	1	2	1	—	2	2	2	1	1	—	2	3	1	7
3—4 »	—	—	1	4	—	—	—	2	3	—	—	1	1	3	—	5
4—5 »	—	—	—	1	—	—	—	—	1	—	—	—	—	1	—	1
5—6 »	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
6—9 »	—	—	—	—	1	—	—	—	—	1	—	—	—	—	1	1
Total	23	33	15	9	5	25	22	21	12	5	15	21	24	21	4	85

Table 21. Cholesterol content of the different zones of the adrenal cortex in premature infants.

Age	Permanent cortex										Foetal cortex					Total number of cases
	Exterior part					Interior part										
	0	+	++	+++	++++	0	+	++	+++	++++	0	+	++	+++	++++	
0—7 days	12	3	7	2	1	8	7	7	3	—	3	8	6	7	1	25
8—14 »	3	1	2	1	1	2	2	1	2	1	3	1	1	2	1	8
Total	15	4	9	3	2	10	9	8	5	1	6	9	7	9	2	33

Table 22. Cholesterol content of the different zones of the adrenal cortex in newborn, fullterm infants.

Duration of disease	Zona glomerulosa					Zona fasciculata					Zona reticularis or foetal cortex					Total number of cases
	0	+	++	+++	++++	0	+	++	+++	++++	0	+	++	+++	++++	
0— 3 days	2	2	1	1	—	3	—	2	1	—	3	—	2	1	—	6
4— 7 »	3	—	4	2	—	3	2	2	2	—	4	—	4	1	—	9
8—15 »	1	1	2	3	1	1	2	3	2	—	1	2	2	3	—	8
15—30 »	1	7	4	1	—	1	4	5	3	—	1	3	5	4	—	13
1 —2 months	1	5	3	5	1	4	—	6	4	1	3	1	4	6	1	15
2 —3 »	2	2	—	3	2	1	2	2	2	2	—	4	1	2	2	9
3 —4 »	—	1	1	4	1	—	1	3	3	—	1	—	2	4	—	7
4 —5 »	2	—	3	1	—	2	1	2	1	—	2	—	2	2	—	6
over 5 »	1	—	2	2	4	2	—	1	2	4	2	—	2	2	3	9
Total	13	18	20	22	9	17	12	26	20	7	17	10	24	25	6	82

Table 23. Miscellaneous material. Cholesterol content of the different cortical zones, grouped by the duration of disease.

Duration of disease	Zona glomerulosa					Zona fasciculata					Zona reticularis or foetal cortex					Total number of cases
	0	+	++	+++	++++	0	+	++	+++	++++	0	+	++	+++	++++	
0— 3 days	2	2	1	—	—	4	1	—	—	—	3	2	—	—	—	5
4— 7 »	2	3	—	2	—	4	2	—	1	—	1	2	2	2	—	7
8—14 »	—	1	—	2	—	1	—	—	2	—	—	1	1	1	—	3
15—30 »	—	9	1	4	1	8	2	2	2	1	4	6	2	2	1	15
1—2 months	2	5	2	3	—	5	—	4	3	—	5	—	4	3	—	12
2— 3 »	—	1	4	—	2	1	2	2	1	1	2	2	1	1	1	7
3— 4 »	—	—	—	1	1	—	1	—	—	1	—	—	1	—	1	2
4— 5 »	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
over 5 »	—	—	—	—	1	—	—	—	—	1	—	—	—	—	1	1
Total	6	21	8	12	5	23	8	8	9	4	15	13	11	9	4	52

Table 24 Gastroenteritis material. Cholesterol content of the different cortical zones, grouped by duration of disease.

mathematically demonstrable, however, by cholesterol staining, with those who died of diarrhoea.

4. No distinct law-like regularity in the lipoid content of the adrenocortical zones is present in the different disease or duration of disease groups.

VIII. THE ADRENALS IN SOME PARTICULAR DISEASES

In the foregoing, only premature infants and diarrhoea patients have been dealt with as separate groups, being numerous enough to allow of mathematical corroboration.

However, there are several diseases peculiar to newborn and to infants in which adrenal changes have often been found. Although these groups are not particularly large in the present material, it may be justifiable to study these cases in slightly greater detail.

Cerebral Deformities

Towards the end of the 19th century, LOMER (1884), and ZANDER (1890), found that patients with anencephalus, congenital hydrocephalus, encephalocele and other cerebral deformities often have unusually small adrenals. The same was observed, particularly with anencephaluses by ELLIOTT & ARMOUR, GOLDZIEHER, EKHOLM & NIEMINEVA. LANDAU explains the small adrenals as being due to the fact that the involution of the foetal cortex is already fairly complete in the foetal period. MCNEILL reports 5 anencephaluses; with one of them only had the involution of the foetal cortex advanced unusually far.

Present Cases.

Table 25 shows the cerebral deformities included in the present material.

The present material includes only one anencephalus, Case No 183/49. The patient also had other deformities, e.g. large cystic

Case No	Age	Diagnosis	Weight of adrenals, g	Average adrenal weight at same age	Foetal cortex %	Average foet. c. % at same age
183/49	20 min.	Anencephalus ...	7.00	6.50±0.37	84	77
56/49	5 days	Meningoencephalocele occipit.	5.83	6.50±0.37	69	65
94/49	2 months	Encephalocele reg. frontalis	2.54	3.51±0.22	42	19
268/48	5½ »	Hydrocephalus	3.80	4.46±0.27	11	8
73/49	5½ »	»	4.37	4.46±0.27	—	8
79/49	6 »	» cong.	4.97	4.69±0.24	—	5
190/49	6 »	»	3.43	4.69±0.24	—	5
147/49	8 »	» cong.	3.35	4.69±0.24	15	5
269/49	9 »	»	6.00	4.67±0.39	—	—
39/49	9 »	» cong.	5.35	4.67±0.39	—	—

Table 25. Cases of cerebral deformity.

kidneys. A fairly extensive haemorrhage could be seen in the adrenals. The involution of the foetal cortex had not advanced any further than usual.

Nor do the size of the adrenals or the involution of the foetal cortex of the other cases differ distinctly from the normal. According to Lomer, a deformity in the anterior part of the brain causes adrenal changes particularly often. Case No. 94/49 belongs to this group. This patient, it is true, had smallish adrenals, but the involution of the foetal cortex was even unusually slow. Hydrocephalus patients, again, were so old at the time of death that their foetal cortex would have practically disappeared in the normal course of events, and hence no conclusions can be drawn from this material.

Congenital Heart Disease

According to GOLDZIEHER (1946), oxygen deficiency causes an enlargement of the adrenals and retards the involution of the foetal cortex. He has found this with several patients who died of congenital heart disease, particularly with cyanotic patients, so-called blue babies.

Present Cases.

The present material includes 15 cases of death from congenital heart disease, and these cases are specified in Table 26.

Case No	Age	Cyanosis	Weight of adrenals, g	Average weight of adrenals at same age	Foetal cortex %	Average foetal cortex % at same age
51/49	1 day	+	4.99	6.50±0.37	69	77
58/49	5 days	+	6.51	6.50±0.37	70	68
130/49	5 »	+	7.15	6.50±0.37	60	60
61/49	9 »	++	4.88	6.11±0.45	46	57
217/48	10 »	++	4.40	6.11±0.45	40	55
66/49	13 »	+++	5.45	6.11±0.45	35	46
45/49	18 »	+	4.25	4.52±0.31	41	38
146/49	1 month	++	3.52	4.30±0.36	13	27
159/49	1½ months	+	3.99	4.30±0.36	50	27
113/49	2½ »	—	4.97	3.51±0.22	12	24
177/49	3 »	++	4.17	4.10±0.28	13	10
224/49	3 »	—	3.52	4.10±0.28	37	10
399/49	4 »	—	3.32	4.03±0.30	30	7
139/49	7½ »	—	4.58	4.69±0.24	—	4
133/49	10½ »	—	3.81	4.67±0.39	—	—

Table 26. Patients who died of congenital heart disease.

From a study of Table 26 it is seen that the weight of the adrenals of these patients does not differ much from the average weight for the same age.

The involution of the foetal cortex was distinctly retarded with three patients (159/49, 224/49 and 399/49). On the other hand it was found in Cases 217/48, 66/49, 146/49 and 113/49 that the involution of the foetal cortex had advanced considerably more than is normal for the same age.

There is no relationship between cyanosis and the large size of the adrenals and retarded involution of the foetal cortex. With particularly cyanotic patients, such as 61/49, 217/48, 66/49, 146/49 and 177/49, the adrenals are relatively small, and the foetal cortex percentage is in all cases under average.

Pyloric Stenosis

In 1919 PIRIE & al. found the adrenals considerably above normal with some patients who had died of congenital pyloric stenosis. DIJKHUIZEN & BEHR. JAUDON (1948), and FANCONI & LANDOLT (1949) later published some similar cases. In spite of being a clinically distinct disease pyloric stenosis could not be demonstrated on obduction in all the cases (FANCONI & LANDOLT, DIJKHUIZEN & BEHR). Histologically an unusually large foetal cortex is sometimes found in the adrenals of these patients. This is closely connected with the so-called adrenogenital syndrome, and differential diagnosis may be difficult particularly with male infants in whom macrogenitosomia has no time to develop if the patients die young of an insufficiency of the other adrenal layers. This insufficiency, again, produces symptoms reminiscent of pyloric stenosis, such as vomiting and dehydration (DIJKHUIZEN & BEHR, JAUDON, BLACKMAN, ALLIBONE & al. 1947, DARROW 1944, CARLGREN, etc.).

Present Cases.

The present material includes 9 patients with clinically and patho-anatomically distinct pyloric stenosis.

Table 27 gives a specification of the cases.

Case No	Age	Duration of disease	Weight of adrenals, g	Average weight of adrenals at the same age	Foetal cortex %	Average foetal cortex % at the same age
247/48	1 1/2 months	1 month	2.90	4.30±0.36	24	26
350/48	» »	»	4.20	4.30±0.36	30	26
96/49	» »	21 days	4.17	4.30±0.36	30	26
169/49	» »	1 1/2 months	4.52	4.30±0.36	34	26
270/48	2 »	»	3.00	3.51±0.22	24	19
274/48	» »	»	2.40	3.51±0.22	26	19
369/48	» »	21 days	4.30	3.51±0.22	34	19
43/49	» »	1 1/2 months	2.85	3.51±0.22	30	19
362/48	5 »	4 1/2 »	4.40	4.64±0.27	20	9

Table 27. Patients with pyloric stenosis.

Table 27 shows that no particularly large adrenals are present in the material. Deviations from the average weight are fairly small, and they are roughly equally frequent in both directions. The foetal cortex percentage, apart from Case 247/48, is somewhat above average. With three patients (369/48, 43/49 and 362/48) this difference distinctly exceeds the normal range of variation. The weights of these adrenals, however, are »normal», and hence these cases cannot be considered, at least not definitely, as representative of the above pathological picture.

On Adrenal Haemorrhages

In 1901 HAMMILL frequently found adrenal haemorrhages in stillbirths. In 1932 GOLDZIEHER & GORDON reported 84 cases of adrenal haemorrhage, 37 of them newborn. With the newborn, extensive haemorrhage produces a typical picture in which respiratory difficulties are the dominant symptom, the so-called pseudopneumonia of the newborn (GOLDZIEHER & GORDON 1930).

Extensive adrenal haemorrhages in connection with septic conditions were first reported by LITTLE (1901). The diagnosis is better known, however, as the WATERHOUSE-FRIEDRICHSEN syndrome. BAMATTER showed in 1934 that the phenomenon is especially peculiar to purulent meningitis caused by meningococcus.

GOLDZIEHER (1946) divides the haemorrhages present in the adrenals into four groups, as follows:

1. *Small haemorrhages*, present in the stroma and lymphatic spaces without tissue destruction.
2. *Diffuse haemorrhagic* infarction without tissue destruction.
3. *Destructive haemorrhages* usually begin from the zona reticularis and gradually transform the adrenal into a haemorrhagic cyst, on the surface of which some cortical tissue is found.
4. *Massive haemorrhage:* the adrenal is transformed into a sac larger than the original organ. The sac is easily ruptured resulting in retroperitoneal haematoma which may rupture into the peritoneum and result in the formation of haemoperitoneum.

Present Cases.

Small haemorrhages without tissue destruction, belonging to Group 1 above, are encountered fairly often, particularly in the area of the foetal cortex. Their significance as a factor disturbing the activity of the adrenals seems unclear on the basis of the present cases, for they were found so often and in cases with the most varied pathological picture.

Types 2 and 4 do not occur in the present material at all. Cases belonging to type 3 are three in number (240/48, 255/48 and 183/49). The significance of adrenal haemorrhage as the cause of death of these patients, however, is not clear. Case 240/48, it is true, died at the age of 6 days with symptoms fairly typical clinically, but on obduction it was found that the patient had »Kernicterus» and extensive pneumonia; hence there were several causes to account for the respiratory difficulties and other symptoms. Case 255/48 died at 3 days of age of pseudomonas aeruginosa septicaemia, and Case 183/49 was an anencephalus that died immediately on birth.

The present material includes 2 patients who died of purulent meningitis caused by meningococcus, but they had no adrenal haemorrhages. Nor have extensive haemorrhages been found in connection with other septic conditions, apart from Case 255/48 mentioned above.

Patients who died of Pseudomonas Aeruginosa Septicaemia.

The present material contains 10 patients who died of septicaemia produced by pseudomonas aeruginosa. Eight of them display a very uniform course of disease, and at death they were roughly of the same age (RANTASALO 1950). It could therefore be assumed that the adrenal findings in these patients were fairly similar. Table 28 gives a specification of the cases.

The first 8 cases of Table 28 evidence the fact that individual differences are so great that no distinct adrenal changes due to the disease can be indicated.

Case No	Age	Duration of disease	Weight of adrenals, g	Average weight of adrenals at the same age	Lipoid content		
					S—R	L—B—S	pol.
255/48	3 days	1 day	7.00	6.50±0.37	+		
142/49	4 »	2 days	5.16	6.50±0.37	+++	+++	++
105/49	5 »	1 day	4.98	6.50±0.37	+	+	+
138/49	5 »	»	12.00	6.50±0.37	++	++	+
114/49	6 »	»	10.75	6.50±0.37	+	+	+
174/49	6 »	»	3.90	6.50±0.37	+	++	+
132/49	7 »	»	5.57	6.50±0.37	+	+	+
100/49	11 »	»	5.62	6.11±0.45	+	++++	++
178/49	22 »	20 days	3.95	4.52±0.31	+++	+++	+++
161/49	1½ months	30 »	4.81	4.30±0.36	++++	++++	++++

Table 28. Patients who died of pseudomonas aeruginosa septicaemia.

Miscellaneous Cases

Lewis & Pappenheimer reported two patients who died of *congenital syphilis*, whose involution of the foetal cortex was retarded. McNeill's material contained 4 such cases but this phenomenon was not present.

The present material contains only one infant who died of congenital syphilis (Case 409/48). The patient was 4 months old at death, the adrenals weighed 4.08 g (average 4.03 g), and the foetal cortex percentage was 25 (average 7); hence the amount of foetal cortex was distinctly above normal.

Sarason found in 1943 that the adrenals of the newborn who had died of *erythroblastosis foetalis* were remarkably large (weight 12—17 g). A couple of similar cases were reported by Allibone & al. (1947). The present material contains 3 of these patients, and their adrenal weights were 6.50, 5.10 and 8.70 g (the average adrenal weights for that age are 6.50 and 6.11 g). One of these three, therefore, had somewhat larger adrenals than the usual, but the deviations from the normal are not as great as those reported by the investigators mentioned.

Chronic adrenal insufficiency, so-called *Addison's disease*, is rare

with children in its typical form. ATKINSON in 1938 reported 40 cases with children, among which two only were under 1 year. In 1946 JAUDON collected from the literature 100 cases of infantile Addison's disease; three of them were under two years. In 1948 SIKL described a clinically typical case of Addison's disease in a child of 33 days, in which a distinct adrenal hypoplasia was found on autopsy. — The present material included no single case of Addison's disease, at least not in its typical form, either clinically or histologically.

Results

The above shows that the adrenal changes considered »typical« of certain disease groups are by no means a constant phenomenon. In most of the groups, it is true, the material available is so limited that no positive conclusions can be drawn. However, the finding, for example, that in the material of 15 cases of patients who died of congenital heart malformation there was no single instance of large adrenals with the large foetal cortex reported by GOLDZIEHER (1946), supports the opinion that this phenomenon is in no way inevitable with these patients.

To summarise the adrenal findings reported above in certain special groups of diseases it can be said that:

1. No particularly small adrenals were found in connection with cerebral deformities (10 cases), nor did the development of their foetal cortex differ from the normal.

2. The size of the adrenals and the foetal cortex of infants who died of congenital heart disease (15 cases) differed to no degree worth mentioning from the average values of the total material. Severe cyanosis seemed to have no influence.

3. No large adrenals, with a large foetal cortex, were found in the pyloric stenosis patients of the present material (9 cases).

4. Fairly extensive haemorrhage in the adrenal cortex was found with three patients, but with none of them was it the only cause of death. The Waterhouse-Friedrichsen Syndrome was not demonstrated once.

5. In the clinically homogenous material of the patients who died of pseudomonas aeruginosa septicaemia (10 cases) great variations were

found in the size and lipoid content of the adrenals of the different individuals.

6. The involution of the foetal cortex was retarded in the single patient of the present material who died of congenital syphilis.

7. It was found that the adrenals of the three patients in the material who died of erythroblastosis foetalis were not distinctly larger than the average.

IX. RELATIONSHIP OF THE ADRENALS TO THE THYMUS

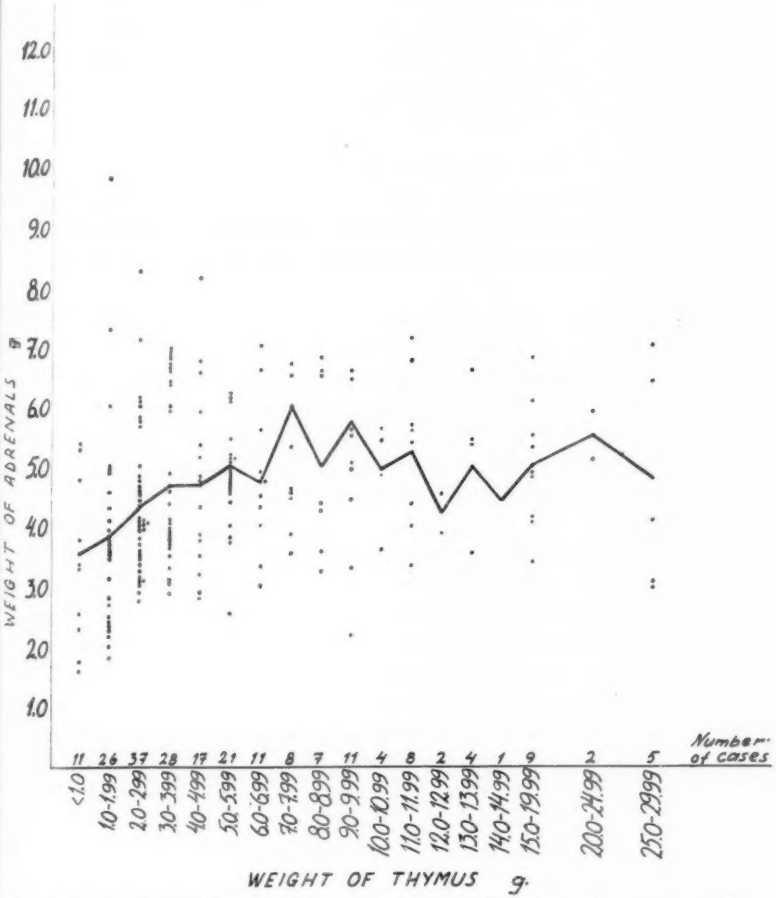
SCHRIDDE (1911) and MATTI (1912) found that hyperplasia of the thymus is often encountered in Addison's disease, and the same observation was also made e.g. by GROLLMAN (1947), VERZÁR (1948), BOYD (1943), GOLDZIEHER (1946), and SELYE (1948). JAFFE (1924), and MARINE et al. (1924), have shown by animal tests that the thymus is enlarged after adrenalectomy.

According to SELYE, the following most important changes of the thymus take place in test animals in the course of the GAS: alarm reaction causes its rapid decrease with the reduction of lymphatic tissue; in the course of the stage of resistance the thymus tends to return to its former size, diminishing rapidly again in the stage of exhaustion.

KEILMANN (1923) studied the relationship of thymus and adrenals in clinical autopsy material, and obtained no distinct correlation. SPOLVERINI (1916) attained the same result. In so-called »thymus death» BOYD has often found adrenal hypoplasia. On the other hand, CH'INK & HSUCH (1941), in a material of still-births and patients who died at birth, found hyperplasia of the thymus and adrenals usually present in one and the same individual.

Present Investigations

The interelationship between the thymus and the adrenals in the patients of the present material is shown in Graph 19. On the basis of this graph it can be stated that adrenals of all sizes are fairly equally divided among all weight groups of the thymus. The smallest



Graph 19. The relationship between the weights of the thymus and the adrenals.

thymuses seem to be accompanied, on the whole, by the smallest adrenals. Hypoplastic adrenals are not present in connection with large thymuses.

The following can be advanced as an explanation of this result:

Large thymuses are usually found in patients who have died of acute diseases, in whom, as is shown by Graph 11, the adrenals also are at their largest. The smallest thymuses again are found in those with diseases of long duration, particularly with patients who die of gastro-enteritis (TÄHKÄ 1951), and they also have, as is shown by Graph 12, the smallest adrenals.

As shown by TÄHKÄ elsewhere, the individual variations in thymus weight are exceedingly great. This makes the drawing of conclusions very difficult indeed, and may account for the contradictory results advanced in literature on the relationship between thymus and adrenals.

X. RELATIONSHIP OF THE ADRENALS TO THE THYROID GLAND

Hoskins (1910), as well as Ingle & Higgins (1938) and Deane & Greep (1947) found that the adrenal gland is enlarged with increasing activity of the thyroid gland. Deane & Greep have shown that hyperthyroidism initially causes cortical hypertrophy, particularly of the zona fasciculata, but signs of exhaustion are often found later. Hypothyroidism, they have found, causes adrenal atrophy.

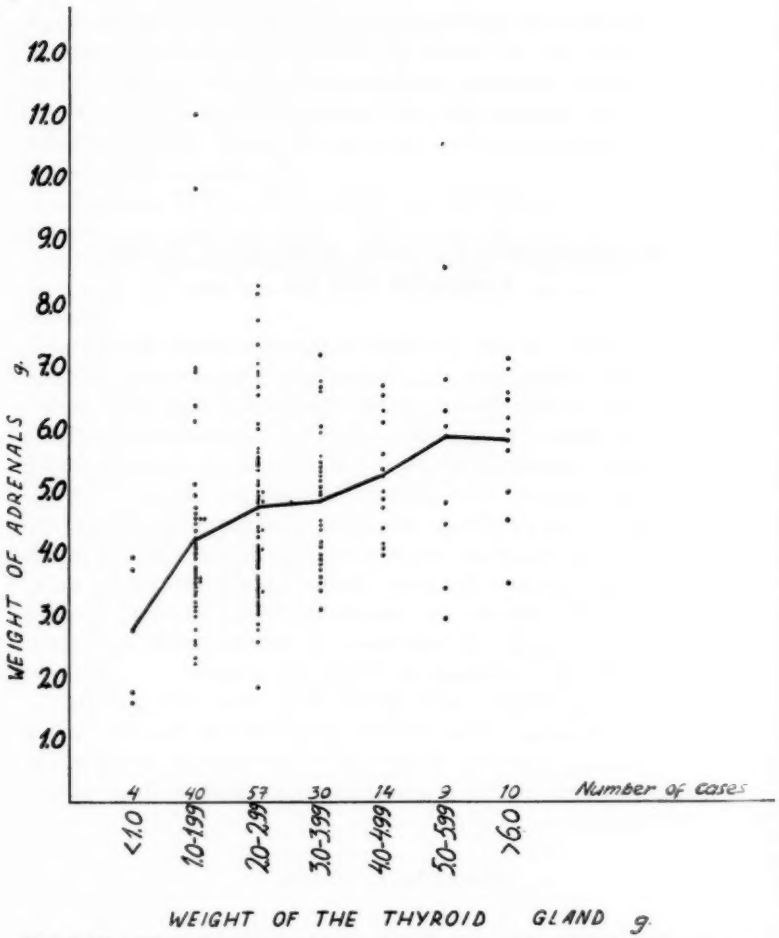
According to Selye (1946, 1947), the changes produced by the GAS in the thyroid gland are not as distinct as those produced in the adrenal and the thymus. However, during the alarm reaction, signs of reduced thyroid activity are sometimes found, while in counter shock and in the stage of resistance its activities are increased. However, no distinct variations in weight are present.

Uotila & Pekkarinen have shown that, with men suffering a rapid death, activation of the thyroid gland can be observed and is expressed both in a rise in weight and in histological changes. In individuals suffering from a disease of longer duration, these phenomena decrease.

Present Investigations

The relationship between the weights of the adrenals and the thyroid gland of the patients of the present material is shown in Graph 20. The curve reveals the average adrenal weight increasing with the increasing weight of the thyroid gland, although exceptions may occur in individual cases.

The thyroid gland weights for the present material are given by Tähkä elsewhere in greater detail. They show that the thyroid gland



Graph 20. The relationship between the weights of the thyroid gland and the adrenals.

is at its largest with patients who have died after a short illness, while with diseases of longer duration its weight decreases somewhat, but the results are not as marked as with the adrenals.

The fact evident from Graph 20, that the weight of the adrenals

and the thyroid gland increase simultaneously, could be explained by attributing the enlargement of the two organs to a common cause. The first cause to suggest itself is the stimulating effect that the tropic hormones of the pituitary exercise on both these organs. However, as the histological structure of the thyroid glands in the present material has not yet been studied, no positive conclusions can be drawn as to the possible parallel fluctuations in the activity of the organs in question.

Cases of Goitre.

UOTILA compared in 1941 the weight and structure of the adrenals and the thyroid glands of the newborn in normal and goitre cases in Finland. In the normal material the average weight of the adrenals was 6.93 g for males and 6.96 g for females, and the corresponding weights of the thyroid gland 2.94 g and 3.33 g. With goitre patients the adrenals weighed, on an average, 8.09 g with males and 8.08 g with females, and the thyroid gland 9.29 g with males and 8.56 g with females. In the histologically most severe cases of goitre the permanent adrenal cortex was unusually small.

ase o	Age	Duration of disease	Diagnosis	Weight of thyroid gland, g	Weight of adrenals, g	Average adrenal weight at same age	Foetal cortex %	Average f.c. % at same age
3/49	20 min.	20 min.	Anencephalus	8.73	7.00	6.50±0.37	84	77
0/49	5 days	5 days	Vitium cordis congenita	6.54	7.15	6.50±0.37	60	65
0/49	11 »	1 day	Septicaemia	7.50	5.62	6.11±0.45	64	55
3/49	28 »	28 days	Haematoma subdurale	6.36	6.15	4.52±0.31	33	27
6/49	1 month	1 month	Vitium cordis congenita	8.02	3.52	4.30±0.36	13	27
4/48	2½ months	1½ months	Gastroenteritis	7.60	4.50	3.51±0.22	18	19
3/49	»	2½ »	Vitium cordis congenita	15.82	4.97	3.51±0.22	12	19
0/48	5½ months	5 months	Tub. miliaris	27.50	6.42	4.64±0.27	11	8
1/49	»	5½ »	Debilitas cong.	19.72	5.95	4.64±0.27	—	8
5/49	»	8 days	Pneumonia	6.57	6.57	4.64±0.27	32	8

Table 29. Cases of congenital goitre.

In the present material 10 patients had goitre, the weight of the thyroid gland exceeding 6 g, considered by LEIDENIUS (1931) and UOTILA (1941) as the goitre limit for Finnish infants. The cases are specified in Table 29.

Table 29 shows that the adrenals generally, in cases of goitre, are larger than the average (exceptions are constituted by Cases 100/49 and 146/49). The average arrived at for the total material is that the adrenal weight for goitre children is 20 % higher than the »normal» weight for the same age. No distinct correlation exists between the size of the goitre and this deviation. Apart from Case 135/49, the amount of the foetal cortex differs fairly little from the mean value for the same age.

This result, hence, is on the same lines as that reported above on the relationship between the weights of thyroid glands of normal size and adrenals.

XI. DISCUSSION

SELYE with his school, SAYERS et al. and numerous other investigators have shown that the most varied range of factors, such as cold, heat, hunger, muscular stresses, poisons, and different infections bring about changes e.g. in the adrenal cortex. In animals, these changes are generally very uniform and conform to relatively firm rules. The adrenal finding in each case is decisively dependent on the kind, intensity and duration of the stress in question.

A study of the adrenal findings in miscellaneous clinical autopsy material gives results that seem very varied. This is in fact evident considering that many simultaneous factors are often at work in the individual cases. Among them may be mentioned the disease proper, the type and intensity of which varies greatly, possible additional diseases, the malnutrition almost regularly present in diseases of long duration in particular, and the strain imposed on the organism by therapeutic measures (e.g. operation), etc. The results are perhaps, in addition, considerably affected by the fact that the starting point in the cases is different. It would seem natural that the reaction of the organism differs with patients where one, on falling ill with his last disease was suffering from malnutrition and had possibly previously experienced a great deal of illness, while the other is a formerly healthy individual in good condition.

Conclusions to be drawn from infant material, are further considerably obscured by the variations in size due to the development of the adrenals, and by the infant's rapid growth at this age.

On the basis of the foregoing it must be stated that hardly any conclusions can be drawn from the adrenal findings observed in individual cases. Instead, the results obtained by age and disease

groups from an extensive material can perhaps be considered as indicative of the course.

When endeavouring to apply the results of animal tests to human material another point to be borne in mind is that reactions in the human organism cannot be immediately assumed as exactly similar to those in animals. As, however, corresponding tests cannot be carried out with men the results of animal tests must be utilised with certain reservations.

On the basis of SELYE's »General Adaptation Syndrome» theory and the results obtained by SAYERS & SAYERS (1948) with test animals, the most usual finding to be expected with the patients of the present material would be large adrenals poor in lipoids. Such, according to SELYE, is the condition of the adrenals at the »stage of exhaustion», and according to SAYERS & SAYERS, when »intense continuous stress has led to death».

With adults ROGERS & WILLIAMS (1948) have often discovered the adrenal findings to be in compliance with the »General Adaptation Syndrome». In Finland, UOTILA & PEKKARINEN have found the same with adults who have died of an acute disease. The adrenal weights of their patients are at their highest in patients who died after a disease of 48 hours, and with the time of reaction extending the size of the adrenals begins to decrease somewhat.

A review of the results obtained from the present material shows that the cases can be divided up, on the basis of adrenal findings, into 3 main groups:

1. With those who died after a disease of short (0—3 and 4—7 days) duration, generally, absolutely and relatively large adrenals, poor in lipoids, are found.

2. In those of the so-called miscellaneous material whose illness has been of lengthy duration, the absolute weight of the adrenals is lower than with the former, differing fairly little, throughout the material, from the normal values. With these patients the relative weight is somewhat increased, and the lipoid content of the cortex increases with the duration of disease extending.

3. With patients who died of gastroenteritis of long duration (over 14 days) the absolute weight of the adrenals is distinctly below the normal, and decreases throughout the material with the duration

of disease increasing. The relative weight of the adrenals with these patients increased somewhat. Lipoid content is fairly abundant and increases with extending duration of disease.

The patients of Group 1, by their adrenal findings, can be said to have died at the shock stage of the alarm reaction or at the stage of exhaustion. According to SAYERS & SAYERS, they would correspond to the above-mentioned Type 3, »intense continuous stres sending in death».

The adrenal finding of the patients in Group 2 corresponds, in the first place, according to SELYE, to adrenals at the resistance stage and to SAYERS & SAYERS Type 2, developing when there is »a very gradual change in the internal or external environment.»

It seems that in these cases, at the time of death, the adrenals are not yet in the exhaustion stage but death has come to the organism in spite of the adrenal cortex still functioning. However, it must be borne in mind that no definite conclusions as to the functioning of the adrenals can be drawn on the basis of their size and lipoid content alone. (ROGERS & WILLIAMS 1947, 1948).

The adrenal finding in Group 3 is reminiscent in the first place of SAYERS & SAYERS's Type 6, in which a small adrenal rich in lipoids is found due to shortage of ACTH developed on the basis of hypopituitarism. Similar adrenals have been described by SELYE in test animals whose hypophysis had been removed a short while previously.

This leads to the assumption that insufficiency of ACTH incretion develops with infants in connection with fatal gastroenteritis of long duration. Possibly the same effect could result in some other disease groups also, but due to the limited range of material it is not demonstrable. One of the reasons why this phenomenon is so marked with diarrhoea patients may be that all the patients that died of chronic diarrhoea had been suffering from malnutrition and had often had to live on insufficient food for several weeks. MULINOS & POMERANTZ (1941) have shown by animal tests that lengthy malnutrition causes adrenal atrophy which, according to MULINOS, POMERANTZ & LOJKIN (1942), can be cured by transplantation of the hypophysis. In 1946 SELYE found that a diet poor in proteins reduces the secretion of ACTH. UEHLINGER (1948) has found changes in man in the anterior pituitary lobe in chronic hunger conditions. — In prolonged gastro-

enteritis, therefore, two different factors, the disease itself and chronic malnutrition, might have a reducing effect on ACTH incretion.

However, the finding — a small adrenal rich in lipoids — can also be explained by the fact that the disease has damaged the adrenal cortex so severely that it can no longer react to ACTH stimulation. Such adrenals, in gastroenteric patients in particular, may be the direct result of the deleterious influences of malnutrition on the adrenal cortex. Hence, SAYERS (1949) found that, on a diet poor in proteins, rats develop small adrenals rich in lipoids, but that there is no concurrent decrease in ACTH incretion.

MAUN, CAHILL & DAVIS's (1945) statement that a prolonged lack of some amino acids may cause adrenal atrophy, as well as the small adrenals found by JACKSON (1915) in chronic hunger, can perhaps be explained by means of the two effect mechanisms. The same applies e.g. to adrenal atrophy present in connection with chronic malaria, as described by GOLDEN etc.

Whether the established adrenal atrophy is a consequence of the lack of ACTH or of direct adrenal lesion is a question that cannot be solved on the basis of the present investigations. Its solution would require experiments in adrenal function.

KERPEL-FRONIUS & VARGA (1949) found general organic atrophy in patients who died of prolonged gastroenteritis. Hence, the suggestion presents itself that the small adrenals found in the present investigation might be a part symptom of this general atrophy of the organs, which again might be due to the fact that the organ governing many of the functions of the organism, the pituitary gland, might be inadequate in its functioning. This theory is supported e.g. by the fact that Simmonds' disease can develop in connection with chronic infectious diseases (HILDEBRAND & RYNEARSON 1943, SELYE 1950). In addition, the weakening of genital functions often encountered in connection with chronic diseases may also be of hypophyseal origin (BERNTH & HAGENS 1944, GUGGISBERG 1946, etc.). The same explanation can perhaps be advanced for ELO's (1945) observation that patients who have died of tuberculosis often display atrophy of the ovaries and of the mucous membranes of the uterus.

To sum up, it can be stated that it seems obvious that the adrenals of infants and young children, in diseases leading to a rapid death, conform in their reaction with the principles of the GAS. In prolonged

cases the adrenal finding corresponds, in the first place, to an organ at the stage of resistance. An exception is constituted by the patients who die of gastroenteritis, who develop adrenal atrophy which can be explained firstly as a part phenomenon of a general exhaustion of the organism probably brought on by insufficiency in the pituitary function.

XII. SUMMARY

The adrenals were removed from 311 infants who had died of different diseases. They were weighed and stained with Delafield's haematoxylin and eosin; Scarlet-red and Liebermann—Burchard—Schultze stainings were made of the frozen sections, and some of them were inspected in polarized light. Variations in the size and lipoid content of the adrenals and the involution of the foetal cortex were observed by age, sex, birth weight, duration of disease and type of disease. In addition, the thymus was removed from 309 patients and the thyroid gland from 244 patients. The weights of these organs were compared with the weights of the adrenals.

The results show the following:

1. The absolute weight of the adrenals decreases from birth to the age of 3 months from 6.50→3.51 g. The weight then rises slowly, without, however, attaining the weight of the newborn by the age of two years. With premature births the absolute values are lower, but the trend of development otherwise is similar.

2. The relative weight of the adrenals decreases continuously from 0 to 2 years. The values are roughly of the same range with full-term infants and premature births.

3. The adrenals grow considerably towards the end of pregnancy.

4. No difference is found between the weights of the adrenals of male and female infants.

5. The considerable decrease of the adrenals in the earliest months of life is probably largely due to the involution of the foetal cortex. At birth the foetal cortex is found to constitute 73 %, and with premature births 77 %, of the whole adrenal cortex. Up to the age of 21 days the foetal cortex decreases fairly regularly, and the involution continues even after that, but the individual variations

are considerable. The connective tissue capsule surrounding the medulla is visible in practically all the patients of the material.

6. In cases where the foetal cortex percentage differs considerably one way or another from the average, no mutual correlation can be demonstrated as regards the type of disease, duration of disease or size of the adrenals.

7. The largest adrenals, on an average, are found with patients who have died of an illness of short duration (0—3 and 4—7 days).

8. With patients who have died of prolonged diarrhoea, the adrenals decrease continuously with extending duration of disease, attaining distinctly sub-normal values. In the so-called miscellaneous material, consisting of other fullterm patients over 14 days of age, the adrenal weight in prolonged cases is more or less unchanged, varying but little to either side of the »normal» values of the material.

9. The relative weights of the adrenals, throughout the material, are higher than normal. However, they do not rise as much as is presupposed e.g. by the loss in weight of chronic gastroenteric patients.

10. Results obtained as regards the lipoid contents of the adrenals, with the three histological determination methods employed, correspond fairly closely. In 19 cases, in addition, it has been possible to compare the results with chemical lipoid determinations. It seems that the chemical and histological lipoid contents are fairly similar.

11. The average lipoid content, by all methods, is smaller in the gastroenteric, premature birth and newborn materials than with patients who have died of other diseases.

12. The results obtained from the total material and by all methods of staining seems to indicate that in patients who have died rapidly the adrenals are poor in lipoids, and that the lipoid content increases with prolonged duration of disease. This fact is mathematically demonstrable in the diarrhoea material only, from results obtained by cholesterol staining.

13. No distinct regularity is present in the variations in the lipoid content of the different zones of the adrenal cortex in the different disease and duration of disease groups.

14. Furthermore, the adrenals have been studied separately in certain disease groups in which, according to the literature, changes are often found. With the patients of the present material who died

of cerebral deformity, congenital heart malformation, pyloric stenosis or erythroblastosis foetalis, adrenals differing greatly from the average cannot be demonstrated. A fairly extensive haemorrhage in the adrenal cortex was found with three patients, but with none of them was this the cause of death, at least not the only cause.

15. No distinct correlation can be shown between the weights of the thymus and the adrenals.

16. The relationship between the weights of the thyroid gland and the adrenals evidences that the average adrenal weight rises as the weight of the thyroid gland increases. Adrenals exceeding the average by some 20 % are found in goitre patients.

17. The many factors affecting the adrenal changes are discussed, with the inference that they make the drawing of conclusions considerably more difficult.

18. It is found that the adrenal finding with children who have died after a short duration of disease appears to correspond in the first place to the shock or exhaustion stage of Selye's »General Adaptation Syndrome». In the miscellaneous material, again, the adrenals, in the first place, seem to be at the »stage of resistance». The small adrenals, rich in lipoids, found in connection with chronic diarrhoeas, must be understood primarily as a result of the lack of ACTH brought about by the disease.

XIII. REFERENCES

ADAMS, E. and BAXTER, M.: Arch. Path. 1948: *48:* 13.

ADDISON, T.: Quoted by Goldzieher 1946.

ALLIBONE, K. J., BAAR, H. S. and CANT, W. H. P.: Arch. Dis. Childh. 1947: *22:* 210.

ARMSTRONG, H. G. and HEIM, J. W.: J. Aviat. Med. 1938: *9:* 92.

ATKINSON, F. R. B.: Brit. J. Childr. Dis. 1938: *35:* 96.

BABES, V.: C.r. Soc. Biol. 1908: *2:* 235.

BAMATTER, F.: Jb. Kinderhk. 1934: *142:* 129.

BARTA, L.: Ann. Paediatr. 1948: *171:* 158.

BENNER, M. C.: Amer. J. Path. 1940: *16:* 787.

BENNETT, H. S.: Amer. J. Anat. 1940: *67:* 151.

BERNTH OG HAGENS: Medicinsk Kompendium. 4. udgave. Store Nordiske Videnskapsboghandel. København 1944.

BEUMER, H.: Mschr. Kinderhk. 1921: *19:* 409.

BLACKMAN, JR, S. S.: Bull. Hopkins Hosp. 1946: *78:* 180.

BLUMENSAAT, C.: Virchows Arch. 1929: *271:* 639.

BORBERG, N. C.: Skand. Arch. Physiol. 1915: *32:* 287.

BOSCOTT, R. J , MANDL, A. M., DANIELLI, J. F. and SHOPPEE, C. W.: Nature (London) 1948: *162:* 572.

BOURNE, G. H : The Mammalian Adrenal Gland. Oxford University Press 1949.

BOYD, W.: Textbook of Pathology, 4th edition. London. Henry Kimpton 1943.

BRUN: Bibl. Laeg. 1939—40: *131:* 197.

CARLGREN, L-E.: Acta Paediatr. 1949: *38:* 71.

CASTALDI, L. and VANNUCCI, D.: Quoted by Krogman: Growth of man. Tabulae Biologicae 1941 vol. 20.

CHAUFFARD, A , LAROCHE, G. and GRIGAUT, A.: C.r. Soc. Biol. 1914: *1:* 529.

CH'INK, Y. and HSUCH, C. S.: Zbl. Kinderhk. 1941: *38:* 377.

CLATWORTHY, H. W. and ANDERSON, R. G.: Amer. J. Dis. Childr. 1944: *67:* 167.

CRAMÉR, H.: Sannolikhets Kalkylen. — Almqvist & Wicksell, Uppsala 1949.

DALTON, A. J. and SELYE, H.: Anat. Rec. Suppl. 1938: *72:* 48.

DARROW, D. C.: J. Pediatr. 1946: *28:* 515.

—•— PRATT, E. C., FLETT, Jr, J., GAMBLE, A. H. and WIESE, H. F.: Pediatrics 1949: *3:* 129.

—•— and SARASON, E. L.: J. clin. Invest. 1944: *23:* 11.

DEANE, H. W. and GREEP, R. O.: Amer. J. Anat. 1946: *79:* 117.
—»— and —»— Endocrinology 1947: *41:* 243.
—»— and MCKIBBIN, J. M.: Endocrinology 1946: *38:* 385.
—»— and SHAW, J. H.: J. Nutrit. 1947: *34:* 1.
—»— —»— and GREEP, R. O.: Endocrinology 1948: *43:* 133.
DEMPSEY, E. W. and WISLOCKI, G. B.: Physiol. Rev. 1946: *26: 1.*
DEUCHER, G. W.: Arch. klin. Chir. 1923: *125:* 578.
DOSNE, C. and DALTON, A. J.: Anat. Rec. 1941: *80:* 211.
DUGUID, J. B. and MILLS, J.: J. Path. a. Bact. 1928: *31:* 721.
EKHOLM, E. and NIEMINEVA, K.: Acta Paediatr. 1950: *39:* 67.
ELLIOT, T. R. and ARMOUR, R. G.: J. Path. a. Bact. 1911: *15:* 481.
—»— and TUCKETT, I.: J. Physiol. 1906: *34:* 332.
ELO, R.: Thesis, Helsinki 1945. Über den Einfluss der Lungentuberkulose auf die Menstruation.
EUSTACHIUS, B.: Quoted by Bourne 1949.
FANCONI, G. and LANDOLT, R. F.: Helvet. paediatr. Acta 1949: *4:* 15.
—»— —»— Ibid. 1949: *4:* 22.
FEULGEN, R. and VOIT, K.: Pflügers Arch. 1924: *206:* 389.
FEX, J.: Biochem. Z. 1920: *104:* 82.
FLEXNER, L. B. and GROLLMAN, A.: Anat. Rec. 1939: *75:* 207.
FORSSELL, P.: Ann. Med. Fenn. 1947: *36:* 247.
—»— Ibid. 1948: *37:* 16.
FRIEDRICHSEN, C.: Jb. Kinderhk. 1918: *87:* 109.
GAMBLE, J. L.: Extracellular Fluid. — Harvard University Press, Cambridge, Mass. 1947.
GOLDEN, A.: Feder. Proc. 1948: *7:* 271.
GOLDZIEHER, M. A.: Wien, klin. Wschr. 1910: *22:* 809.
—»— Endocrinology 1934: *18:* 179.
—»— The Adrenal Glands in Health and Disease. Philadelphia. F. A. Davis Co 1946.
—»— and GORDON, M. B.: Klin. Wschr. 1930: *12:* 270.
—»— —»— Endocrinology 1932: *16:* 165.
GRAHAM, G. S.: J. med. Res. 1916: *34:* 241.
GROLLMAN, A.: The Adrenals. — The Williams & Wilkins Co. Baltimore 1936.
GUGGISBERG, H.: Lehrbuch der Gynäkologie. — Verlag von S. Karger in Basel 1946.
HAILMAN, H. F.: Endocrinology 1944: *34:* 187.
HALLMAN, N.: To be published.
—»— and AHVENAINEN, E. K.: Ann. Med. Fenn. 1950: Suppl. 7.
—»— and TÄHKÄ, H.: Ann. Med. Fenn. 1950: *39:* 95.
HAMMILL, S. M.: Arch. Pediatr. 1901: *18:* 161.
HARTMAN, F. A. and BROWNELL, K. A.: The Adrenal Gland. — London. Henry Kimpton 1949.
HASNER, E.: Acta chir. Scand. 1949: *92:* 51.

HENCH, PH. S., KENDALL, E. C., SLOCUMB, C. H. and POLLEY, H. F.: Proc. Staff. Meet. Mayo Clin. 1949: *24:* 181.
HENI, F.: Z. exper. Med. 1941: *108:* 427.
HERMANN, O.: Mschr. Kinderhk. 1940: *82:* 76.
HETT, J.: Z. mikrosk.-anat. Forsch. 1925: *3:* 179.
HILDEBRAND, A. G. and RYNEARSON, E. H.: Arch. int. Med. 1943: *71:* 262.
HOSKINS, R. G.: J. A. M. A. 1910: *55:* 1724.
HOWARD, E.: Anat. Rec. 1940: *77:* 181.
HUEBSCHMANN: Zbl. Path. 1921: *31:* 568.
INGLE, D. J. and HIGGINS, G. M.: Endocrinology 1938: *23:* 419.
JACKSON, C. M.: Amer. J. Anat. 1909: *9:* 119.
—»— Ibid. 1915: *18:* 75.
—»— Ibid. 1919: *25:* 221.
JAFFÉ, H. L.: J. exper. Med. 1924: *40:* 325.
—»— Ibid. 1924: *40:* 619.
JAUDON, J. C.: J. Pediatr. 1946: *28:* 737.
KAPPERT, A.: Helvet. med. Acta 1947: *14:* 5.
KARWICKA,: M. D. Beitr. path. Anat. 1911: *50:*. 437.
KAWAMURA, R.: Die Cholesteriesterverfettung. Jena, Gustav Fischer 1911.
KAY, W. W. and WHITEHEAD, R.: J. Path. a. Bact. 1935: *41:* 293.
KEENE, M. F. L. and HEWER, E. E.: J. Anat. 1927: *61:* 302.
KEILMANN, K.: Z. Kinderhk. 1923: *35:* 25.
KELLNER, B.: Zbl. Path. 1933: *57:* 407.
KERN, H.: Dtsch. med. Wschr. 1911: *21:* 971.
KERPEL-FRONIUS, E. and VARGA, F.: Pediatrics 1949: *4:* 301.
KNOUFF, R. A., BROWN, J. B. and SCHNEIDER, B. M.: Anat. Rec. 1941: *79:* 17.
KOLMER, W.: Arch. mikrosk. Anat. 1918: *91:* 1.
z. LAGE, H.: Mschr. Kinderhk. 1940: *82:* 91.
LANDAU, M.: Dtsch. med. Wschr. 1913: *7:* 300.
—»— Ibid. 1913: *12:* 546.
LEIDENIUS, L.: Acta Soc. Medic. fenn. Duodecim. Ser. B. Tom. XVI, 1931.
LEWIS, R. W. and PAPPENHEIMER, A. M.: J. med. Res. 1916: *34:* 81.
LIEBEGOTT, G.: Beitr. path. Anat. 1944: *109:* 93.
LITTLE, E. G.: Quoted by Goldzieher 1946.
LOESCHKE, E.: Münch. med. Wschr. 1910: *57:* 48.
LOMER, R.: Virchows Arch. 1884: *98:* 366.
LONG, C. N. H.: Recent Progress in Hormone Research, I: 99: 1947.
MACLEAN, A.: J. Hyg. 1937: *37:* 345.
MACLEAN, A. B., SULLIVAN, R. C. and ZWEMER, R. L.: Amer. J. Dis. Childr. 1932: *43:* 1277.
MARINE, D., MANLEY, O. T. and BAUMANN, E. J.: J. Exper. Med. 1924: *40:* 429.
MATERNA, A. and JANUSCHKE, E.: Virchows Arch. 1927: *263:* 537.
MATTI, H.: Mitt. Grenzgeb. Med. u. Chir. 1912: 24.
MAUN, M. E., CAHILL, W. H. and DAVIS, R. M.: Arch. Path. 1945: *39:* 294.
—»— —»— —»— Ibid. 1945: *40:* 173.

McNeill, M.: Ulster med. J. 1947: *16:* 41.
Menten, M. L. and Smith, M. P.: Amer. J. Dis. Childr. 1936: *52:* 54.
Meyer, R.: Virchows Arch. 1912: *210:* 158.
Moon, V. H.: Quoted by Selye 1950.
Mulinos, M. G. and Pomerantz, L.: Amer. J. Physiol. 1941: *132:* 368.
Mulinos, M. G., Pomerantz, L. and Lojkin, M. E.: Endocrinology 1942 *31:* 276.
Neymann, N.: Arch. Gynäk. 1939: *168:* 79.
Nichols, J. and Hill, Ch.: Arch. Path. 1948: *45:* 717.
Oppenheim, R. and Loeper, M.: C.r. Soc. Biol. 1901: *53:* 318.
—»— —»— Ibid. 1903: *55:* 330.
Pfeiffer, H.: Z. exper. Med. 1919: *10:* 1.
Pirie, G. R., Tor, M. B. and Lond, M. R. C.: Lancet 1919: *2:* 513.
Plecnick, J.: Arch. mikrosk. Anat. u. Entw. gesch. 1902: *60:* 414.
Rantasalo, I.: Lecture delivered at the meeting of Finnish Pediatrics Society on 6. 5. 1950.
Rich, A. R.: Bull. Hopkins Hosp. 1944: *74:* 1.
Rogers, Ph. V. and Richter, C. P.: Endocrinology 1948: *42:* 46.
Rogers, W. F. and Williams, R. H.: Arch. Path. 1947: *44:* 126.
—»— —»— Ibid. 1948: *46:* 451.
Romeis, B.: Taschenbuch der mikroskopischen Technik, 14 Auflage München und Berlin 1943.
Rominger, E.: Ann. Paediatr. 1948: *171:* 344.
Rosenbaum, P.: Z. Kinderhk. 1931: *51:* 70.
Sarason, E. L.: Arch. int. Med. 1943: *71:* 702.
—»— Arch. Path. 1943: *35:* 373.
Sayers, G.: J. Clin. Endocrinol. 1949: *9:* 656.
—»— and Sayers, M. A.: Recent Progress in Hormone Research II: 81: 1948.
—»— Sayers, M. A, Fry, E. G., White, A. and Long, C. N. H.: Yale J. Biol. a. Med. 1943—44: *16:* 361.
Scammon, R. E.: Proc. Soc. exper. Biol. a. Med. 1926: *23:* 809.
Scheel, O.: Virhows Arch. 1908: *192:* 494.
Schilf, F.: Z. Konstit. lehre 1922: *8:* 507.
Schoenheimer and Sperry, W. M.: J. biol. Chem. 1934: *106:* 745.
Schridde, H.: L. Aschoff: Pathologische Anatomie, 2. Aufl. Gustav Fischer, Jena 1911.
Selye, H.: Endocrinology 1937: *21:* 347.
—»— J. Clin. Endocrinol. 1946: *6:* 117.
—»— Textbook of Endocrinology, Second Edition, Acta Endocrinologica Inc. Montreal, Canada 1949.
—»— The Physiology and Pathology of Exposure to STRESS. Acta, Inc. Medical Publishers. Montreal, Canada 1950.
Siki, H.: J. Path. a. Bact. 1948: *60:* 323.
Simmons, K. and Todd, T. W.: Growth 1938: *2: 93.*
Spolverini, M.: Arch. Kinderhk. 1916: *65:* 130.

STARKEL, S. and WEGRZYNOWSKI, L.: Arch. Anat. u. Entw. gesch. 1910: 214.
STEPHANI, E.: Jb. Kinderhk. 1923: *101:* 201.
SWINYARD, C. A.: Anat. Rec. 1940: *76:* 69.
— — Ibid. 1943: *87:* 141.
v. SZASZ, A.: Mschr. Kinderhk. 1939: *79:* 332.
— — Ibid. 1941: *88:* 307.
THADDEA, S.: Erg. inn. Med. 1938: *54:* 753.
THOMAS, E.: Beitr. path. Anat. 1911: *50:* 283.
TOBECK, A.: Virchows Arch. 1928: *267:* 690.
TAHKÄ, H.: To be published in Acta Paediatr.
— — —»— —»—
UEHLINGER, E.: Quoted by Yearbook of Endocrinology, Metabolism and Nutrition. 1948: 29.
— — Quoted by Selye 1950.
UOTILA, U. U.: Duodecim 1940, Suppl. 2.
— — Acta Soc. Medic. fenn. Duodecim. Ser. B. Tom. XXX fasc. 3: 50, 1941.
— — and PEKKARINEN, A.: Acta endocrinol. 1951: *6:* 23.
VEREZÁR, F.: Lehrbuch der Inneren Sekretion. Liestal 1948.
VIRCHOW, R.: Arch. path. Anat. 1857: *12:* 481.
WATERHOUSE, R.: Lancet 1911: *1:* 577.
WELTMANN, O.: Beitr. path. Anat. 1913: *56:* 278.
ZANDER, R.: Beitr. path. Anat. 1890: *7:* 439.
ZWEMER, R. L.: Amer. J. Path. 1936: *12:* 107.

MEDICAL LIBRARY

Acta Paediatrica

Vol. 40 · May 1951 · Suppl. 82

UNIVERSITY
OF MICHIGAN
FEB 13 1952
MEDICAL
LIBRARY

STUDIES OF THE RENAL EXCRETION OF P^{32} IN INFANCY AND CHILDHOOD

BY

LARS STRÖM

Almqvist & Wiksells Boktryckeri AB UPPSALA

List of Supplements to Acta Pædiatrica.

1. **Muhl, Greta,** Über den Stoffwechsel des gesunden, natürlich ernährten Säuglings und dessen Beeinflussung durch Fettreduktion der Nahrung. Sw. Cr. 5: —.
2. **Höjer, J. Axel,** Studies in Scurvy. Sw. Cr. 5: —.
3. **Eriksson, Zaida,** Über Anstaltsschaden der Kinder: »Hospitalismus» in Kinderheimen. Sw. Cr. 3: —.
4. **Drucker, Paul,** Clinical Investigations into the Pathogenesis of Infantile Tetany. Sw. Cr. 3: —.
5. **Wallgren, Arvid,** Contribution à l'étude des splénomégalies de l'enfance. Sw. Cr. 5: —.
6. **Rhodin, Hans,** The Suspension-Stability of the Blood in Scarlatina. Sw. Cr. 3: —.
7. The Proceedings of the Fourth Scandinavian Pædiatric Congress, held at Helsingfors on June 28th—30th, 1927. Sw. Cr. 5: —.
8. **Herlitz, C. W.,** Studien über die Blutzuckerregulierung bei gesunden Säuglingen und solchen mit exsudativer Diathese. Sw. Cr. 3: —.
9. **Widnäs, Karin,** Études sur le diabète sucré chez l'enfant. Sw. Cr. 5: —.
10. **Gyllenswärd, Curt,** Some Sources of Error at Differential Count of White Corpuscles in Blood Stained Smears. Sw. Cr. 3: —.
11. **Salomonsen, Leif,** Periodisches Erbrechen und Ketonämie bei Kindern. Sw. Cr. 5: —.
12. **Wallgren, Arvid,** Erfahrungen über epidemischen Icterus (sog. Icterus catarrhalis). Sw. Cr. 5: —.
13. **Rietz, Einar,** Sterblichkeit und Todesursachen in den Kinderjahren. Sw. Cr. 5: —.
14. **Gyllenswärd, Curt,** Das weisse Blutbild bei Hunger und regelmässiger Nahrungszufuhr. Sw. Cr. 3: —.
15. **Skaar, T.,** Experimental Rickets. Sw. Cr. 5: —.
16. **Toverud, Kirsten Utheim,** and **Toverud, Guttorm,** Studies on the Mineral Metabolism during Pregnancy and Lactation and its Bearing on the Disposition to Rickets and Dental Caries. Sw. Cr. 5: —.
17. **Kloster, Johan,** The Distribution and Frequency of Rickets in one of the Fishery Districts of Finmark and Relation of Diet to the Disorder. Sw. Cr. 5: —.
18. **Svensgaard, Elisabeth,** Blood Sugar in Normal and Sick Children with Special Reference to Coeliac Disease. Sw. Cr. 5: —.
19. **Herlitz, C. W.,** A Contribution to the Knowledge of the Function of the Liver and the Reticulo-Endothelial System, Particularly in Infectious Diseases of Children. Sw. Cr. 3: —.
20. **Henschen, Folke,** Über Christians Syndrom und dessen Beziehungen zur allgemeinen Xanthomatose. Sw. Cr. 3: —.
21. **Bjørn-Hansen, Haakon,** Leukozyten-Untersuchungen bei den Masern. Sw. Cr. 5: —.
22. **Joukovsky, V. P.,** et **Rousskikh, V. N.,** Étude clinique et anatomo-pathologique sur la tuberculose des centres nerveux chez l'enfant. Sw. Cr. 3: —.
23. **Huss, Ragnar,** Studien über die Schultz-Charltonsche Auslöschreaktion bei Scharlach. Sw. Cr. 5: —.
24. **Wickström, J.,** Eine elektrokardiographische Untersuchung über das Herz beim Scharlach. Sw. Cr. 3: —.
25. **Schiøtz, Carl,** Eine Darstellung und kritische Bewertung der Ursachen des Rückganges der Säuglingssterblichkeit in Norwegen. Sw. Cr. 5: —.
26. The Proceedings of the Sixth Northern Pediatric Congress, Stockholm August 27—August 29, 1934. Sw. Cr. 5: —.
27. **Rustung, Erling,** Studien über Rachitis. I. Mitteilung. Sw. Cr. 3: —.
28. **Sundal, Alfred,** Chronische infektiöse Erkrankungen der Harnwege im Kindesalter. Sw. Cr. 3: —.
29. **Magnusson, J. Henning,** Zur Kenntnis der Blutveränderungen bei Frühgeborenen. Sw. Cr. 5: —.
30. **Herlitz, C. W.,** Studien über den Krankheitsverlauf und die Therapie des Diabetes mellitus bei Kindern. **Söderling, B.,** Behandlung der Zuckerkrankheit im Kindesalter ohne Diäteinschränkungen. Sw. Cr. 5: —.
31. **Ström, Justus.** Periodisches Erbrechen mit Ketonämie bei Kindern. Sw. Cr. 5: —.
32. **Faxén, Nils,** The Red Blood Picture in Healthy Infants. Sw. Cr. 5: —.
33. **Herlitz, Gillis,** Studien über die Prognose der okkulten Kindertuberkulose. Eine Nachuntersuchung bei tuberkulinpositiven und tuberkulinnegativen Kindern. Sw. Cr. 5: —.

FROM THE PAEDIATRIC CLINIC OF KAROLINSKA INSTITUTET
AT THE NORRTULL'S HOSPITAL, STOCKHOLM, SWEDEN
HEAD: PROFESSOR ARVID WALLGREN

Studies of the renal excretion of P^{32} in infancy and childhood

BY

LARS STRÖM

Also published as Supplement 82 to volume 40, 1951
of Acta Pædiatrica

Translated from the Swedish by
ULLA SCHÖTT

AB J. O. ÖBERG & SONS BOKTRYCKERI, ESKILSTUNA 1951
Printed in Sweden

To the memory of my father

Preface

To Professor Arvid Wallgren, who has for several years been my superior and teacher at the Paediatric Clinic at the Norrtull's Hospital, I extend my warmest thanks for his never failing encouragement and patience during this work.

The experimental part of the investigations were carried out in a large extent in the Department of Metabolic Research at Wenner-Gren's Institute. For all working facilities given to me I would express my thanks to the Head of this Department Docent J. Möllerström. For invaluable help with all problems, arising during the work and for all discussions about the theoretical questions, I wish to thank Docent O. Lindberg.

It is also a pleasant duty for me to offer my hearty thanks

to all them, who have assisted me in the practical work: Amanuens L. Ernster, Mr B. Boström and Mr F. Ponikiewski,

to Mr G. Blom, M. A., for his valuable help with the statistical treatment of the material

to Dr J. C. Peterson, for valuable discussions and generous help with the medical terminology in English.

to Mr R. Jörgensen for drawing the curves and graphs.

to Dr Gun Carlström and to Dr Maj Danielsson for collaborations with the clinical part in some sections of this work

to all my collegues at the hospital and to all members of the nursing staff.

The investigation was performed with financial support from Statens Medicinska forskningsråd.

Stockholm, April 1951. Lars Ström.

CONTENTS

Preface

Introduction

Chapter I. *Review of literature* 9
- Glomerular filtration
- Active and passive tubular reabsorption
- Present opinion concerning the renal function
- The renal excretion of phosphate

Chapter II. *Choice of methods* 18
- Radioactive phosphate
- Safeguards in the use of isotopes
- Blood phosphorus
- Urinary phosphorus
- Definitions

Chapter III. *The present investigation* 24
- Clinical experiments and methods
- Determination of phosphate in blood and urine
- Determination of radioactivity
- Results

Chapter IV. *The material* 30

Chapter V. *The renal excretion of P^{32} in normal conditions* 32
- Own investigations of normal individuals
- Discussion

Chapter VI. *The renal excretion of P^{32} in pathological conditions* 42
- Discussion

Chapter VII. *The kidney function in prematures* 60
- Survey of the literature
- Phosphate clearance
- Observations on the renal excretion of P^{32} in prematures

Chapter VIII. *The kidney function in diabetic children* 69
- Survey of the literature
- Present investigations

Chapter IX. *General discussion and conclusions* 82

Summary

Case reports

Bibliography

Introduction

The present work originated from certain observations made at the Wenner-Gren Institute in Stockholm (MÖLLERSTRÖM, LINDBERG). An investigation in diabetics of the resorption, metabolism and excretion of perorally administered radioactive phosphorus showed, on the one hand, that the specific activity of the urine was for the most part greater than that of the blood and, on the other, that, when this did *not* occur, the patients had clinical symptoms of renal damage. From this I conceived the possibility of using radioactive phosphorus as a medium for testing and determining the renal function in cases of renal damage. The test, as conceived, does not fall clearly into anyone of the usual groups of quantitative renal function tests. In the course of these investigations there have appeared new aspects, the scope widening to include phosphate excretion through the kidneys in a more general sense.

I have, however, tried to limit my task to the primary question of ascertaining whether the mentioned observations would give a new possibility of determining the renal function. From a pediatric point of view, the investigation is of particular interest, because acute renal diseases, of common etiology, occurs more generally in the earliest years of life. Furthermore I thought it should be useful to compare the result of such an investigation with other usual renal tests.

The notable fact that the specific activity of the urine in healthy persons, after an injection of radioactive phosphorus, is so much higher than that of plasma, has throughout been kept in view. In the course of the present investigation, new works have appeared confirming this observation (GOVAERTS, ÖSTLING, FRIEDLÄNDER, WILDE, and others).

CHAPTER I

Review of literature

In his fascinating book, "Lectures on the Kidney", HOMER W. SMITH quotes a French chemist, *Fourcroy,* who defines the physiological significance of urinary investigations in the following words:

"The urine of man is one of the animal matters that have been most examined by chemists and of which the examination has at the same time furnished the most singular discoveries to chemistry, and the most useful applications to physiology as well as the art of treating. This liquid which commonly inspires men only with contempt and disgust, which is generally ranked amongst vile and repulsive matter, has become, in the hands of the chemists, a source of important discoveries and is an object in the history of which we find the most singular disparity between the ideas which are generally formed of it in the world, and the valuable notion which the study of it affords to the physiologist, the physician and the philosopher."

These words were written close upon 150 years ago, and still this source of important discoveries shows no signs of becoming exhausted. The reverse happens.

In the course of time, the conceptions held by physiologists of the renal function and urinary secretion, have been embodied in a long series of theories. BOWMAN (1842), LUDWIG (1844) and HEIDENHAIN (1874), have been followed by CUSHNY (1926) and VOLHARD (1931), AMBARD, REHBERG (1926) EKEHORN (1931) and SMITH (1937). The actual significance of all these theories is not that they elucidate the problem of renal function, but rather in the fact that they have stimulated further research. A great deal has gradually become illuminated, but renal physiology still offers a large field for research.

GLOMERULAR FILTRATION

WEARN's and RICHARDS' investigations of fluid from the glomerular capsule simultaneously with bladder urine in the frog, have provided a solid basis for establishing some essential features of renal physiology. Glomerular urine is practically free from protein, as a result of a filtration process. The effective filtration pressure is the resultant of the blood pressure in the glomerular capillary and the colloid osmotic pressure in the blood plasma and the pressure in Bowman's capsule, the latter two acting in the opposite direction.

This work by WEARN and RICHARDS and others, substantiates the hypothesis of glomerular filtration proposed by LUDWIG. In amphibians, studies have shown that the pH, vapor pressure, conductivity and concentrations of urea, glucose, chloride, inorganic phosphorus, exogenous uric acid, exogenous creatinine, bicarbonate, etc, are practically identical in the glomerular fluid and the protein-free serum filtrate. These observations indicate that, at least in certain amphibians, the glomerulus acts merely as an ultrafilter.

In certain circumstances, such as, orthostatism, physical exertion, renal disease or increased plasmatic protein concentration, the plasma protein is, apparently, filtered through the glomeruli in larger quantities than normally, and protein will then be found in the bladder urine. BRANDT and GRUHN, as well as LIPPMAN, have, however, shown that the presence of protein in bladder urine may also be due to a reduced reabsorption in the tubules (tubular reabsorption). Albumin is often found in infants, aged from two to five days, and likewise, and even more constantly, in the urine of prematures (SMITH C. A. 1946). Some albumin is, very likely, normally filtered through the glomeruli to be reabsorbed in the tubules in Man. Such renewed resorption is less marked, or non-existent, in prematures and newborns.

On the other hand, when the blood flow is reduced, the filtration diminishes with a retention of waste products, *i. e.* the following factor lower the effective filtration pressure: 1st, decreasing the glomerular blood pressure, 2nd, increasing the plasma oncotic pressure or: 3rd, increasing the capsular pressure.

GÉRARD applies the term *athrocytosis* to indicate the intracellular flocculation that follows the absorption of electronegative colloids and their storage in the brush border segment of the tubules. Evidently,

the reabsorption through the tubuli of colloidal particles differs from that of crystalloids.

ACTIVE AND PASSIVE TUBULAR REABSORPTION

The reabsorption of water, which in the human kidney produces a urine of a higher osmotic pressure than that of plasma, is supposed to be due, at least partly, to an *active* reabsorption. When a concentration ratio, *i. e.* urinary concentration: plasma concentration, of any solute is different from 1, either it, or the water, or both, may be undergoing an active reabsorption. This is presumed to be brought about through an expenditure of metabolic energy by the tubules (WOLF).

A solution that freely diffuses through the tubular walls is reabsorbed *passively*. The reabsorption of, *e. g.*, acetone is supposed to take place passively, probably also urea (SHANNON).

Contrary to the reabsorption, *tubular secretion* involves a transport of substance from the plasma to the tubular fluid. The fact that a secretion actually occurs, has been well demonstrated by MARSHALL and VICKERS with phenol red, though CUSHNY has tried to refute this. PITTS et al. have suggested a pseudosecretory mechanism by means of which sodium ions are taken up by the tubular cells from the tubular fluid, in exchange for hydrogen ions given up to the tubular fluid. The phosphate ion is likewise reabsorbed.

Through the tubular function, the glomerular filtrate is concentrated 98—99 per cent. LUDWIG regarded this process as a diffusion, but later investigators have shown it to be a more complicated process. WEARN demonstrated that the glomerular urine of the frog, after an injection of glucose, contains a reducing substance which is not present in the bladder urine. Phlorhizin renders the tubules non functional and prevents reabsorption. In the opinion of LUNDSGAARD, the reabsorption depends on a phosphoric regulation process in the tubules which is inhibited by the phlorhizin, and since this substance is more concentrated in the kidney than in any other organ, its effect is strongest there.

Thus, if the function of the renal glomeruli may be regarded as that of ultrafiltration (protein-free filtrate of the bloodplasma), the function of the tubular epithelium may be regarded as, chiefly, a "selective" reabsorption. However, there is evidence that certain of the urinary constituents pass from the blood into the urine at some point in the

tubules beyond the glomeruli (creatinine, ammonia, diodrast, phenol red and hippuran). Inasmuch as the average rate of glomerular filtration is 120—130 cc per minute, it follows that more than 170 litres are filtered through the glomeruli from the plasma daily, the tubules subsequently reabsorbing about 168.5 litres of water, 1 000 gm of NaCl, 360 gm of $NaHCO_3$, 170 gm of glucose and smaller amounts of phosphate, sulfate, amino acids, urea, etc., in order to excrete about 60 gm of Na Cl, urea and other waste products in about 1 500 cc. of urine (HOMER W. SMITH).

REHBERG divides the glomerular filtrates into 3 groups, according to their behaviour from the point of view of the reabsorption process, as follows:

1. Substances that are being actively reabsorbed, i. e., apart from phosphates and sulfates, the forementioned high threshold substances. These substances occur in lower concentrations in the urine, and in higher concentrations in the reabsorbed fluid, than in plasma.

2. Substances that pass back through the tubular epithelium by means of a simple diffusion process, once their concentration in the tubular fluid exceeds the plasma concentration. They correspond to the low threshold substances. They are reabsorbed passively. These substances are never to be found in lower concentrations in the urine, or in higher concentrations in the reabsorbed fluid, than in plasma.

3. No-threshold substances that suffer neither active reabsorption nor any back diffusion. They are, therefore, absent from the reabsorbed fluid.

At a low plasma concentration, inorganic phosphate is almost completely reabsorbed, but even a slight increase in the plasma concentration will make it appear in the urine.

Tubular secretion has always formed a burning subject. Without entering into the various hypotheses, the known data may be summarized as follows: although dyes, creatinine, diodrast, etc., are excreted through the proximal tubules of the mammalian kidney (except creatinine which is not excreted through the kidney in dogs) this process probably plays but an insignificant part under normal conditions, being, possibly, only a functional relic from a more primitive stage. The urea filtration is reduced in acute nephritis where the glomeruli are affected by inflammation, but it remains intact in lipoid rephrosis where the glomeruli are unimpaired or inconsiderably damaged. On the other

hand, the primary excretory function of the tubules may be altered in chronic nephritis with glomerular damages, and function quite differently than the healthy kidneys.

PRESENT OPINION CONCERNING THE KIDNEY FUNCTION

After the investigations of recent years, chiefly American (by SHANNON 1936, ELSOM, BOTT and SHIELS 1936, SMITH 1937, and others), we are able to summarize the renal function as a result of the following fundamental processes (HOGEMAN 1948):

1. Ultrafiltration in the glomeruli of a protein-free solution containing all the substances freely dissolved in the plasma, in the same concentration as in the plasma, with the exception of the small difference due to the Donnan-effect.

2. Active reabsorption in the tubules of the larger part of this filtrate, *i. e.* water and other substances necessary for metabolism or for the maintenance of the electrolyte balance in the body.

3. Passive rediffusion of certain substances through the tubules, this diffusion being entirely dependent on the degree of concentration of the respective substances in the tubular urine and on its diffusibility.

4. Active secretion through the tubular cells of other substances, either normally present in the plasma or artificially administered.

5. A synthesis of certain substances in the kidney.

By means of these processes, the kidneys perform their various tasks, i. e. to remove from the body waste matter and other unwanted substances, and to regulate the water balance and the osmotic equilibrium between the blood plasma and the tissue fluids, as well as the acid-base equilibrium.

Such quantitive renal function tests as are in practical clinical use belong to one or the other of the following four groups: retention tests, concentration-dilution tests, excretion tests and clearance tests (WOLF). These tests supplement one another in so far as a clinician can hardly do without any of them, and tests pertaining to any single group will fail to produce a clear picture of the renal function. The literature on renal physiology is enormous. Above, I have tried to give a short résumé without any pretension to completeness. Detailed accounts of

the quantitative renal function tests will be found in HOMER W. SMITH's Monographs (1937, 1943), ADDIS' book on Glomerular nephritis (1948), A. V. WOLF's "The Urinary Function of the Kidney" (1950), HOGEMAN's excellent survey of the clearance tests (1948), EKEHORN (1945, 1946), LAAKE (1945), HILDEN (1946), JOSEPHSON (1947), RAASCHOU (1948) and HOOD (1949).

THE RENAL EXCRETION OF PHOSPHATE

The phosphate excretion plays an important part in the regulation of the phosphate concentration in the body fluids.

WALKER & HUDSON have shown in frogs, that the plasma phosphate is filtered through the glomerular membranes. They also noted that, in certain circumstances, an active reabsorption takes place in the proximal parts of the tubules and that the urine in the distal parts and in the bladder may be almost free from phosphate. There was no suggestion that phosphate is excreted through the tubular wall. In experiments on dogs, PITTS has demonstrated that the phosphate clearance increases with the plasma phosphate. With a normal phosphate level in the blood, the urine is almost free from phosphate and only a small part of the phosphate that is filtered through the glomerulus is found in the urine.

The process of the reabsorption of glucose has been elucidated by SHANNON and FISHER, GOVAERTS and MULLER and SHANNON, FARBER and TROAST. Apparently, a reabsorption of phosphate takes place also in mammals during the passage of the glomerular filtrate. HARRISON and HARRISON have studied the way in which the excretion of phosphate is controlled and influenced by vitamin D and the parathyroid hormone. They used dogs as test animals, finding that, under standard conditions, there is a limiting maximal rate of reabsorption of phosphate by the renal tubules, which does not vary when the plasma is elevated by the administration of phosphate salts. The phosphate in the glomerular filtrate, over the maximal quantity that can be reabsorbed by the tubules, is excreted with the urine. After an administration of vitamin D to young dogs that had been kept on a rachitogenic diet, a conspicuous rise in the maximal rate of reabsorption of phosphate by the renal tubules was noted, thus increasing the concentration of inorganic phosphate in the plasma, at equilibrium. This effect remains noticeable for 24 hours

after an administration of vitamin D. In the opinion of the forementioned authors, it constitutes an important factor in the antirachitic activity of the organism. The parathyroid hormone has an entirely contrary affect. In a work of 1947, LAMBERT, VAN KESSEL and LEPLAT have found a complete conformity between the excretion mechanism for inorganic phosphate and glucose, respectively, in Man. Both for glucose and phosphate a urinary threshold is to be found. The concept of a renal threshold is attributed to BERNARD (1877) and GOTTLIEB and MAGNUS (1900). They assumed that glucose was excreted in the urine when the plasma level of a certain substance exceeded a critical value which they called the threshold concentration. CUSHNY defines the renal threshold of excretion as the plasma value above which the substance appears in the urine, and below which it does not appear in the urine in any perceptible quantities. The threshold for phosphate in dogs is 1.1—1.5 mM/l acc. (PITTS). The term threshold of retention indicates the value at which the concentration of urine and plasma are identical (WOLF). The threshold of retention is not invariably the same as a normal plasma concentration. Urea and acetone exemplify no-threshold substances. Their concentration ratio constantly equals or > 1, while threshold substances may possess a concentration ratio above or below 1.

Water, chloride, and sugar are quite obviously reabsorbed from the filtrate during the passage along the tubules. The term high threshold substances has been applied (CUSHNY 1926) to such substances, as glucose, amino acids, sodium, potassium and calcium, which are, to a comparatively large extent, absorbed with water and, consequently, absent from the urine, or present only in low concentrations. They appear in the urine in greater amounts when their concentrations in the plasma rise beyond a certain optimal threshold. Glycemia in diabetes is an instance.

The phosphates belong to the low threshold substances that are highly concentrated in the urine, since they are reabsorbed in relatively small amounts or not at all. Other low threshold substances are urea, uric acid, and sulfates, which are reabsorbed in varying amounts.

Inorganic phosphorus is reabsorbed in the proximal tubule like sugar, sodium, chloride and sulfur. In its transfer across the tubular membrane, phosphorylation of the glucose molecule appears to be a necessary preliminary step. The change is brought about by a specific enzyme, a kidney phosphorylase. Dephosphorylation of the hexose phosphate

thus formed, is effected by a second enzyme, "alkaline" phosphatase, present in the cells of the proximal convoluted tubules.

Despite intense researches of recent years, the mechanism of phosphorus excretion can not, as yet, be said to be elucidated. BRULL and his collaborators showed, as early as in 1928, that the excretion threshold of plasma phosphorus is not fixed to any definite value but that, wiht various factors, it can be raised or lowered. BRULL later (1936) demonstrated that injected phosphorus is partly transformed into colloidal phosphorus (colloidal calcium phosphate) which the kidney is unable to excrete. In his important investigations, GOVAERTS, by applying an isotope technique, showed that the formation of colloidal phosphorus does not constitute the only transformation that phosphorus is subject to in plasma. He used the increased urine isotope ratio as evidence of a non-filtrable plasma fraction. His results, in experiments with radioactive calcium, deny the role of a non-filtrable calcium phosphate. In his opinion, the non-filtrable phosphate of plasma consists of some other, labile, phosphate complex which is very slowly synthesized under an enzymatic influence. He concludes that endogenous and exogenous phosphorus are treated differently by the kidneys, possibly because of the different physicochemical nature of the two different phosphorus fractions. GOVAERTS' results were substantiated by the observations of Östling, who gave P^{32} intravenously to patients with renal diseases. Separate urine samples were taken from both kidneys by simultaneous ureteral catheterization. He obtained a different P^{32}/P^{31} ratio from the diseased and healthy kidney in the same patient.

LAMBERT, VAN KESSEL and LEPLAT (1947) have raised certain objections to GOVAERTS' conception. GOVAERTS' determinations from plasma and urine were made simultaneously but during a period when the plasma phosphate was not constant, but was decreasing rapidly, in a relatively unphysiologic condition. It is uncertain whether an artificial raising of the blood phosphate level beyond a certain value is followed by the appearance in the blood of a colloidal, non-filtrable phospho-calcium complex. As yet, sufficient light has not been shed on the mechanism of excretion and reabsorption of organic phosphate under the condition of a constant blood phosphate level. These authors studied the urinary excretion in man in groups with different blood phosphate levels, viz. less than 65 mg per litre, 100 mg per litre and values above 100, respectively. In the first group the phosphate resorption was found to increase

with rising amounts of blood phosphate. In the second group, they noted a threshold for maximal phosphate resorption, where the amount of phosphate reabsorbed from the glomerular filtrate remained constant. In the third group, they actually noticed a non-filtrable phosphate fraction which increased with the rising blood phosphorus and corresponded to the collodial calcium phosphate. Within the limits imposed by this third finding, the urinary excretion of phosphorus appears to conform to laws analogous to those for glucose.

In order to study the renal excretion from one side at a time Swedin has employed the technique with radioactive phosphorus. He made the observation that the kidneys seem to alternate in their function, with other words not always functioning with equal intensity at a given time.

Quite recently, FRIEDLÄNDER and WILDE (1951) applied isotope methods to studies of the urine isotope ratio in inorganic phosphate. They determined the ratio of the isotopes collected in the urine during a definite period, comparing it with the ratio of the isotopes in the plasma, as averaged for the same period. They also fixed the acid-soluble phosphate fraction in the urine and the blood, finding that the urine receives 2—5 times the amount of labelled phosphorus predicted from the plasma ratio; a result identical with GOVAERTS'. Various explanations were suggested without offering any definite solution of the question.

CHAPTER II

Choice of methods

RADIOACTIVE PHOSPHATE

The new biochemical technique of using substances labelled with isotopes has provided more opportunities than ever before for studying vital processes without disturbing their course. We are in a position to follow the exchange of a substance between two media, through a biologic membrane or between the different phases of a proceeding chemical process without interfering with the chemical progress.

The techniques of applying isotopes in biochemistry have become generally known, the pioneers being HEVESY and his collaborators (HEVESY 1940, 1947 and 1948, CHAIKOFF 1942, KAMEN 1947).

Isotopes are variants of an element, differing from one another in the structure of the atom nuclei. The isotopes cannot be separated from one another by any chemical method, but they can by physical methods. As far as our present knowledge goes, their physiologic properties are identical.

When a substance, with a certain amount of a suitable isotope is administered to a living organism, it is possible to trace and follow the molecules of this substance and their varying phases in the organism. But more important is the fact, already mentioned, that the normal processes are not interfered with. The labelled substance is given in a wholly negligible amount. The labelled molecules meet with the same fate as the unlabelled ones. The distribution of the labelled substance and the change in its chemical compound furnish a picture of what happens to the unlabelled molecules of the same substance during the same time.

Among the labelled isotopes now in use in biochemical research, the phosphorus isotope P^{32} has been used most effensively and has been

adapted for a variety of observations. It has proved particularly suitable because of its properties: it is easy to prepare, it has a convenient half life, its radiation is well-adapted for analysis (HEVESY 1940—47), and most importantly is the fact that phosphorus has an important general biologic importance.

Inorganic phosphate introduced into the organism is not exchanged for organically bound phosphate except through the degradation and resynthesis of the organic compound in question (HEVESY 1940). Therefore when some labelled phosphorus is found in an organic compound, that compound must have been synthesized in the course of the experiment. If no labelled phosphorus compound is found it has not been during the time of observation subjected to resynthesis. The content of a recently introduced phosphorus in organic phosphate esters will give a measure of the intensity with which the carbohydrate degradation proceeds, and this will, in its turn, shed light on the energy providing turnover in the tissue or the organ in question.

Studies of the phosphate excretion by means of radioactive isotopes have been carried out earlier by GOVAERTS (1947, 1948) ÖSTLING (1950) and others.

SAFEGUARDS IN THE USE OF ISOTOPES

As a matter of course, the utmost care, has to be taken to avoid such doses of radioactivity as might prove harmful to the recipient, especially as far as children are concerned. Recently, attention has more and more been drawn to the risks inherent in the use of isotopes.

It is difficult to determine the tolerance limits for internally administered isotopes, since regard must be paid to many factors, such as absorption, tissue concentration, exchange and interchange between the various tissues and elimination. Some isotopes are selectively deposited in certain organs, or systems of organs. The distribution can be influenced by pathologic conditions, etc. When the isotopes emits only beta-particles, the action is confined to the regions of selective uptake, since the range of beta-particles in tissue is only a few millimetres. On account of these difficulties in the determination of the tolerance doses in internal administration of radio-isotopes, no definite dosage standards exist. Tolerance doses have been suggested by MARINELLI, QUIMBY and HINE, MORGAN, and others, and, according to these authors

"the safe tracer concentration is an amount that will result in a whole body or whole organ dose of 0.1 rep. (Roentgen equivalent—physical) during the first 24 hours following an administration due to beta-radiation alone". A more recent recommendation is 0.3 rep per week (LOW-BEER). This tolerance is supposed to satisfy theoretic demands for safety. In certain instances, a safe tracer amount may be too small to allow a test to be performed successfully. In the opinion of LOW-BEER, no isotope with a half-life longer than 60 days should be applied to human individuals for clinical, diagnostic or tracer studies. In the present investigation, a dose of 2 microcuries per kg of body weight has been employed. Such a dosage should meet all the requisites for a safe tracer concentration.

BLOOD PHOSPHORUS

Phosphorus occurs in the blood in four forms, viz, inorganic phosphorus (orthophosphate) and the following three organic compounds.

1. Ester phosphorus (diphosphoglycerate, adenosinetriphosphate, hexose phosphate, glycerophosphate).

2. Lipid phosphorus (the phosphatides licithin, cephalin, sphingomyelin).

3. Nucleic acid phosphorus (this fraction, negligible in normal human blood).

The phosphorus of blood is separable into two classes:

a. The acid-soluble, which includes inorganic phosphorus and ester phosphorus.

b. Alcohol-ether soluble, i.e. lipid phosphorus.

The first group is extracted from blood by precipitating the proteins with trichloracetic acid and filtering them. The filtrate then contains phosphorus. Upon extration of blood with alcohol-ether the lipid phosphorus is obtained. The ester, or organic acid-soluble phosphorus, is obtained by determining the total acid soluble P and subtracting from it the inorganic phosphorus.

Phosphorus occurs in the plasma as well as in the blood corpuscles.

In the present investigation, attention is attracted in the first place to the plasma phosphorus, since we are concerned here with the excretion of phosphorus from plasma into urine. The plasma contains acid-soluble phosphorus principally in the form of orthophosphate. In

addition there is a small amount of an organic fraction in the trichloracetic acid extract. The exact quantity of it is stated somewhat differently by different authors. The maximun seems to be less than 0,5 mg % (GUEST and RAPOPORT 1941). During the period of the experiment, less than 4 hours, the amount of renewal of organic phosphorus has been very small, and it has, therefore, been disregarded as a source of the urinary phosphate. Whether the organic phosphate at all passes through a biologic membrane, may well be questioned.

According to KROGH, the organic phosphate does not seem to penetrate the walls of the blood corpuscles.

The concentrations of orthophosphate in plasma vary from one individual to another, as well as from time to time in one and the same individual. Variations have been observed even during the relatively short space of time, 2—3 hours, occupied by the experiments.

Also, the values stated in the literature vary a great deal. Values from some investigations will be found in Table 1.

TABLE 1

Phosphate in blood mg per 100 ml

Author	Plasma (p) or serums (s)	Subject	Remarks
Duke-Elder (1927)	(s) 7.0	horse	inorg. P.
Tron (1928)	(s) 4.7	ox	inorg. P.
Winternitz & Stary (1942)	(s) 3.25	horse	inorg. P.
Walker (1933)	2.9—4.5	man	inorg. P.
Kinsey & Grant (1942)	(p) 4.9—8.05	rabbit	inorg. P.
Hevesy & Hahn (1942)	3.5	man	inorg. P.
Palm (1948)	(p) 6.25	rabbit	inorg. P.

In children and young persons, the phosphorus level in the plasma lies from 1 to 3 mg % above that of adults.

In renal insufficiency, the organic phosphorus in the plasma and cells and the ester phosphorus (diphosphoglycerate) in the cells are greatly increased.

The inorganic and ester phosphorus are reduced in rickets but a rapid increase accompanies the healing process. The inorganic phosphorus is diminished after the injection of insulin.

URINARY PHOSPHORUS

The source of inorganic phosphorus in the urine is chiefly to be found in the plasma phosphorus, though some may, possibly, derive from a hydrolysis of phosphoric acid esters through influence from phosphatase in the kidneys.

In an ordinary and well balanced diet, the urinary phosphates constitute about 60 per cent of the total excretion of phosphorus. When the calcium decreases, the phosphorus excretion will proportionately increase.

Phosphorus occurs in the urine partly in the form of a mono-sodium and a sodium biphosphate, NaH_2PO_4 and Na_2HPO_4, and, to a very small extent, the corresponding potassium salts. About three fourths of the total urinary phosphorus exist in these forms. An insignificant fraction is possibly to be noted also as $(NH_4)_2PO_4$. The remaining fourth of the total phosphate consists of $Ca(H_2PO_4)_2$ and $Mg(H_2PO_4)_2$. These phosphates are precipitated in an insoluble state in alkaline urine, as a result of bacterial action.

The total amount of phosphates in the urine increases under various conditions, such as a lowered alkali reserve, starvation, a high protein diet, severe muscular exercise, in gout and after administrations of large doses of parathyroid extract. The urinary P is low in the morning, increases during the day, reaching its maximum during the night. The principal part of the urinary phosphorus derives from the inorganic P of the plasma. A small portion, about 6 per cent, is organic (glycerophosphates, hexosephosphates, nucleotides).

The kidney abounds in phosphates, notwithstanding the fact that no considerable part of the inorganic P of the urine appears to be formed by any action of this enzyme of organic phosphorus compounds or the plasma, the urinary phosphorus is reduced, when the alkali reserve is high, as during pregnancy and in cases of renal insufficiency, tetany and certain skeletal diseases. Insulin causes a striking reduction in the urinary phosphorus during the first 6 hours after an injection.

DEFINITIONS

The nomenclature applied to radioactive isotopes, in particular P^{32}, is now beginning to be well-known through the various publications of CHAIKOFF 1942, KAMEN 1947, HEVESY 1948 and LOW-BEER 1950. Here will be given some definitions of the terms employed in connection with the isotope technique and which are used in this paper. The definitions are partly given by PALM 1948.

Activity in a sample indicates the presence of a labelled substance. Its magnitude is given by the intensity of the radiation emitted (for P^{32} β —rays). It is expressed as the number of counts per minute recorded from the sample in a given measuring set-up. In the present paper A_b = the activity of a blood sample, and A_u = the activity of a urine sample.

The specific activity is the activity per unit weight of the material in question. In the case of phosphate it is expressed as the number of counts per 0.001 gm phosphorus. In the paper is S_b = the specific activity of the plasma and S_u = the specific activity of the urine.

The precursor is generally the substance from which a chemical compound receives its labelled group. This term is employed when the compound and its precursor constitute different stages in a chemical process as well as when they are the same substance, though separated by, for example, a biological membrane.

The renewal or *the turnover rate* denotes the proportion of a substance, e.g. the phosphate in a given fraction, that is replaced by new substance per minute.

CHAPTER III

The present investigation

CLINICAL EXPERIMENTS AND METHODS

The present investigations were performed on hospitalized children. The children had been fasting, when the investigation was initiated, though allowed to drink water, 200—400 cc, according to age. Phosphate, labelled P^{32}, was administered intravenously in the form of $Na_2\ HPO_4$. Physiologically negligible amounts of the labelled phosphate were given in physiologic salt solution, in order to obtain an easily manageable dose. The amount of radioactivity varied somewhat, from a maximum of 50 microcuries for the bigger children to proportionally less for the smaller ones; about 2 microcuries per kg of body weight. The concentration of the administered phosphate in the blood plasma was observed, at short intervals, for the subsequent 2 or 3 hours. The time intervals varied slightly. In the course of the experiments the most suitable intervals gradually became clear. I made a particular point of concentrating the sampling to the 30—90 minutes after the injection. The samples were capillary blood, extracted by finger puncture. It proved easy to obtain a minimum of 0.4 cc of blood from one puncture. Duplicate samples were as a rule taken by assistants; the two samples being extracted simultaneously from fingers of different hands. The samples were taken in tubes treated with heparin after they had been carefully cleaned with acid.

Urine samples were obtained by catheterization, after preliminary evacuation of the bladder and when possible at the same time the blood was obtained. The latter occasionally took some time, and minor modifications in the sampling have, therefore, been unavoidable.

Minor deviations from this technique are to be noted in Group N_1, where the labelled phosphate was given intraperitoneally, and in Group S where venous samples were substituted for capillary blood.

DETERMINATION OF PHOSPHATE IN BLOOD AND URINE

Determinations of ortho-phosphate in blood and urine were performed according to a routine method used at the Wenner-Gren Institute, specifically the Fiske-Subbarow method with Brigg's modification as described by LINDBERG (1946).

After immediate centrifugation, 0.2 ml of plasma was treated with 10 per cent trichloracetic acid, filtered and diluted with water to a known volume (15 or 25 ml).

To 5 ml of the dilution was added 1 ml of each of the following reagents with careful mixing after each addition.

Reagents: Solution 1: 30 ml conc. H_2SO_4 is diluted with water to 100 ml.
» 2: 10 gm ammonium molybdate is dissolved in water and diluted to 100 ml.
» 3: 20 gm Na_2SO_3 + 0.5 gm hydroquinone are dissolved in water and diluted to 100 ml.

After 30 minutes, the blue colour obtained is read off with a photometer using an S. 75 filter.

Within the various groups, (see chapter IV) I have obtained the following mean values. In group N_2 are the adults excluded.

TABLE 2

Orthophosphate in plasma mg per 100 ml

Group	Mean value	Standard dev.	Number of cases
N_1	7.9 ± 0.36	1.4	15
N_2	5.3 ± 0.41	1.7	23
G	6.1 ± 0.43	2.2	26
N_2K	4.7 ± 0.66	2.3	12

The random error of the phosphate determinations of the plasma was estimated from the examination of 112 duplicates. The determinations were, somewhat arbitrarily, divided into two groups as shown in the table.

Blood sample	n	s
< 0.2 cc	45	0.26
$\geqq 0.2$ cc	67	0.21

The error in each group was estimated by the formula:

$$s = \sqrt{\frac{\Sigma d^2}{2n}}$$

where n = number of pairs and d = difference between the duplicates. In the first group one pair with very great difference was excluded. The error of method appears to be somewhat greater when the amount of plasma is small but the difference may be due to random fluctuations and is, in any case, so small that it can be disregarded.

As the amount of phosphorus in the plasma mostly lies in the interval 4—10 mg per 100 ml plasma, it can be inferred that the relative error ε_p of the phosphorus determinations can be expected to vary between.

$$100 \frac{0.26}{4} = 6.5\ \% \text{ and } 100 \frac{0.21}{10} = 2.1\ \%$$

In the sequel we shall, as an average, use $\varepsilon_p = \pm 5\ \%$. This figure is a reasonable expression of reliability of the determinations.

DETERMINATION OF RADIOACTIVITY

Since the ortho-phosphate forms too small a part of the sample to be precipitated quantitatively, a known amount of $Na_2 HPO_4$ was added in such a way as to enlarge the total amount in the sample to a constant. All ortho-phosphate was then precipitated as $Mg\ NH_4\ PO_4$. The quantities remaining in the solution are so small, in proportion to the precipitate, that they may be ignored.

One ml of the solution is mixed with 5 ml of phosphate solution (18.32 gm of $Na_2HPO_4 + 2\ H_2O$ per litre). The mixture is diluted, in a 50 ml retort, to 30 ml. To this diluted solution 20 ml of Fiske solution (350 gm of citric acid, dissolved in 700 ml of warm water, add 26 gm of Mg O and filter. After cooling, the solution is diluted with 25 per cent of NH_3 to 4 litres) are added. Fine, easily filtrable crystals of $Mg\ NH_4PO_4$ will then appear.

The sample is left overnight, then filtered in a perforated aluminium cup, in which a filter, moistened with 2.5 per cent ammonia, is placed. The technique of this filtration has been described in detail by LINDBERG (1946). The radioactivity is then determined in the usual way, with a Geiger-Müller tube.

On the sample about 1 000 counts are determined and from this figure the value of counts/min. (C.P.M.) is easily obtained.

The background is estimated for a period of 30 minutes.

The radioactivity in the urine was, as a rule, determined in the same manner, unless otherwise stated. The amount of organic phosphate in the urine is so insignificant, if at all existent, that all phosphate in the urine can be regarded as ortho-phosphate. In the latest determinations, the activity was, therefore, usually made directly on the urine, 0.2 ml of the urine being pipetted to the aluminium cup and dried under a lamp. The activity was then determined.

In some instances, the total of phosphate in blood and urine was determined. In these cases, the blood after being hemolyzed in distilled water (0.4 ml of blood + 2.6 ml of distilled water) was oxidized with concentrated sulphuric acid. The resultant extract was diluted to 15 or 25 ml and 5 ml of the dilution was taken for phosphate determination and 1 ml for activity determination.

The error of the method of activity determinations can be estimated theoretically as far as the error caused by the Geiger-Müller counter is concerned. It has been confirmed by many scientists that the number of particles recorded by the counter during a constant time period can be regarded as a Poisson variable provided that the activity is so low that the resolving time can be neglected. We assume that, in a certain determination, sample + background give rise to x counts during t minutes so that the activity per minute is $R = x/t$. We further assume that the background activity is y counts during time u or $B = y/u$ C.P.M. The estimated activity of the sample is then $x/t - y/u$ C.P.M. with the standard error $\sqrt{x/t^2 + y/u^2}$. In our case, $x = 1000$ counts and $u = 30$ minutes. Thus, we find that the relative standard error, which we denote by ε_a, can be written as

$$\varepsilon_a = \frac{1}{R-B} \sqrt{\frac{R^2}{1000} + \frac{B}{30}}$$

In Table 3, $100\ \varepsilon_a$ has been tabulated for some different values of R—B and B.

TABLE 3

Standard error of the activity determination in % of estimated sample strength R—B. R = activity of sample + background in C.P.M., B = activity of background in C.P.M.

	B						
R—B	5	10	15	20	30	40	50
10	6.3	8.6	11	13	16	20	23
15	5.0	6.5	7.9	9.2	12	14	16
20	4.5	5.6	6.6	7.5	9.3	11	13
30	3.9	4.6	5.3	5.9	7.1	8.3	9.5
40	3.7	4.2	4.7	5.2	6.2	7.0	7.8
50	3.6	4.0	4.3	4.7	5.4	6.1	6.8
100	3.3	3.5	3.7	3.9	4.2	4.6	4.9
200	3.2	3.3	3.4	3.5	3.6	3.8	3.9

If the activity is to be estimated with, e.g., 10 % accuracy (with 95 per cent confidence), the relative standard error should be less than about 5 %. It is seen from the table that when the background activity is, e.g., 30 C.P.M., the activity of the sample should then not be less than about 60 C.P.M.

To satisfy this degree of accuracy it is necessary that the activity of the sample be great enough so that values below the dividing line in the table will be obtained.

In the material presented in this thesis, the above requirement is amply fulfilled in the case of the activity determination of urine samples. The accuracy of the determination of blood activity varies considerably. An inspection of the material shows, however, that about 70—80 % of the activity determinations made of samples taken 30—90 minutes after the injection give rise to ε_a values which are less than 5%.

The statistical calculations of the error of the method are also to some extent affected by the variability in the electron tube which cannot be avoided.

RESULTS

A typical example is demonstrated in Table 4.

TABLE 4

Case 23 S. R. N. G. 782/49 17.3.50

Intravenous injection of 0.05 ml P^{32}							
Time	Plasma Orthophosphate			Time	Urine Orthophosphate		
	P	I	I/P		P	I	I/P
8.10	72	225	3.1	8.10	405	670	1.7
8.25	71	283	4.0	8.25	498	2141	4.3
8.40	65	191	2.9	8.40	524	2504	4.8
8.55	61	179	2.9	8.55	191	645	3.4
9.25	62	142	2.3	9.25	138	300	2.2
9.55	60	91	1.5	9.55	119	264	2.2
10.50	55	134	2.4	10.50	456	504	1.1

P = ɣ Orthophospate / cc
I = counts / min / cc
I/P = Specific activity

Altogether about 200 tests were performed. The results of the first year's investigations have, however, been excluded, as a uniform method had not at that time been worked out. To begin with, determinations of total phosphate, as well as orthophosphate, in blood and urine were regularly performed. Later, the investigations were limited to the orthophosphate, this being more essential. The results will be further discussed separately, in the various groups.

CHAPTER IV

The material

The investigation has been performed on 96 children, most of them hospitalized at Norrtull's Children's Hospital, during the period of 1947—1950, and 5 adults. The group distribution will appear below.

Group N2 consists of children with normal renal function. It comprises 18 children aged 1—14 years, most of them had healed primary tuberculosis. They had no clinical signs of any proceeding disease, were afebrile, with a normal or, possibly, a subnormal sedimentation rate. The age, sex and diagnosis will be seen from Table 7. Five normal adults were examined. (Table 8.)

Group N1 consists of 15 prematures aged 3—29 days and with birth weights of between 880 and 2.400 gm. On the time of the examination, they were completely healthy and since have continued to develop normally. The age, sex, weight and general condition will appear from Table 18. The cases are discussed in greater detail in Chapter VII.

Group G includes 20 cases of nephritis in an acute phase. The age and sex and general symptomatology are given in Table 11. All children had albumin in their urine. The sediment varied, though it was in all instances pathologic. The criteria for judging the sediment to be abnormal was whether or not the member of casts and cellular elements exceeded the normal values established by Addis. Fifteen of the children had a retention of non-protein nitrogen. The blood pressure was elevated in 11 cases. Manifest edema was noted in only 3 cases. In this group, no clearance, were performed. In 12 cases concentration and dilution tests were made. The type of disease, onset and course, will be seen from the forementioned Table 11.

Group F includes cases of acute nephritis where there was an oppor-

tunity to make several determinations on one and the same child. That this has not been applied to any considerable extent, is due chiefly to the fact that the interval between 2 determinations must not be too short. At least 3 weeks are required to allow sufficient decay of the isotope so that it will not influence the result of a subsequent determination. The disease period, as well as the time of treatment, was in most of the children too brief to allow repetition of the observations.

In this group, 16 determinations have been made on 7 children, as will be seen from Table 13. The first examination was done during the acute stage. The children are, therefore, at the time of the first examination comparable with those of Group G. In the statistical calculations, this first examination of all the 7 children has accordingly been included in Group G. The disease symptoms appear in Table 13.

Group N_2K consists of children who, at the time of the examination, were in a late healing stage of acute nephritis, the albumin had disappeared from the urine, though in 5 of them there was still an abnormal urinary sediment, 6 still had an elevation of non-protein nitrogen and in 4 there was a persistent hypertension. (Table 12.)

Group C consisted of 5 cases of nephropathies, not classifiable in any of the forementioned groups. They are separately discussed. The duration and actual symptoms of the disease appear from Table 16.

Group S covers 23 cases of diabetes. They form part of an investigation, carried out during the previous year, and still continuing, of all diabetic children, being followed at this hospital treated with a free diet. The purpose of the investigation is to arrive at a comprehensive view of their condition, especially with regard to the renal function. In these cases, inulin and paraminohippurate clearances were performed simultaneously. Three of these cases showed definite clinical signs of renal damage. Retinopathy occurred in 4 cases, 2 of which showed no signs of renal damage. An account of this group is to be found in Table 21. They are more closely described in Chapter VIII.

CHAPTER V

The renal excretion of P^{32} in normal conditions

From the works of Hevesy and his co-workers, we now have good knowledge of how phosphate, introduced into the body, enters and leaves the blood circulation and is distributed into the tissues. Table 5 and 6.

The dispersion of the phosphate in the organism will be seen from the Table 5, according to HEVESY. The dispersion does probably not differ markedly from one mammalian to another. I had occasion to inject P^{32} in a dying child with a severe hernia cerebri and after its death, two hours later, I had opportunity to observe the dispersion in the different organs. The values will be found in Table 6.

TABLE 5

Distribution of P^{32} between different organs of rat four hours after subcutaneous injection of labelled phosphate.

	Spec. activity
Bones	0.020
Muscles	0.191
Liver	0.475
Digestive tract	0.365
Skin	0.192
Lungs and heart	0.317
Blood	0.558
Kidneys	0.370
Spleen	0.256
Brain	0.032

TABLE 6

The distribution of P^{32} in different organs of a human being, 2 hours after an intravenous injection of labelled phosphate.

	Spec. activity
Muscles	0.275
Liver	0.394
Lungs	0.329
Kidneys	0.470
Spleen	0.480
Hypophysis	0.271
Suprarenal glands	0.352
Blood	0.310
Urine	5.450

The P^{32} content of the plasma after intravenous injection decreases very rapidly. The amount of labelled phosphate, excreted by human subjects within the first 24 hours through the kidneys, has been found to vary between 4 and 23 % of the dose injected intravenously (Erf, Tuttle and Lawrence). Govaerts and Lambrechts found that 2,53 % of the P^{32}, injected intravenously into humans, was eliminated by the urine in the first 4 hours. Govaerts found that during the first minutes following intravenous injection of massive doses of labelled phosphate in dogs, the specific activity of the acid-soluble urine phosphorus was appreciably higher than the specific activity of the acid-soluble plasma phosphorus.

The balance of phosphorus intake and excretion is of course also dependent upon the excretion by the bowels. The specific activity of the faeces phosphorus is only 22 % of the specific activity of the urine phosphorus; therefore, the faeces phosphorus to a large extent must have originated from unabsorbed food, which is the only source of nonactive phosphorus. The phosphorus excreted through the kidneys constitutes about twice the loss through the bowels. This study of the excretion of phosphorus by the bowels is in details carried out by Kjerulf-Jensen.

TABLE 7

Group N_2. 18 normal children

Date	No. of case	Initials	Age	Weight in kg	ESR in mm per hr	Hb in g %	Urine	Cl_p	Diagnosis
4.2.47	1. G. 103/47	H. H.	10	25.5	8	11.5	0	6.5	Undulant feber
7.2.47	2. G. 98/47	P. S. E.	7	24.5	5	11.6	0	8.6	Observation
9.4.47	3. F. 172/47	B. C.	14	66.5	12	13.5	0	4.7	Psychoneurosis
14.4.47	4. F. 204/47	R. P.	9	31.4	49	83	0	7.5	Primary pulmonary tuberculosis
14.4.47	5. F. 138/47	A. L.	7	20.8	30	11.6	0	4.4	»
26.4.47	6. F. 271/47	I. N.	15	63.8	6	11.5	0	4.7	Scoliosis
12.6.47	7. G. 335/47	S. L.	15	51.5	10	15.5	0	12.2	Primary pulmonary tuberculosis
12.2.48	8. F. 723/47	G. N.	13	53.2	9	12.5	0	13.9	»
22.1.49	9. F. 675/48	B. K.	12	42.5	19	13.9	0	9.1	»
29.1.49	10. F. 199/47	L. J.	12	44.6	12	13.7	0	7.3	»
19.2.49	11. F. 550/48	E. K.	12	30.6	19	14.6	0	6.2	»
27.2.49	12. F. 654/48	M. L.	13	52.5	30	12.8	0	0.2	» [1]
8.3.49	13. G. 74/49	B. J.	13	37.5	15	13.9	0	8.2	»
21.3.49	14. G. 183/49	H. O. A.	10	39	10	9.5	0	13.1	Meckels diverticel
22.3.49	15. F. 456/46	U. A.	3	12.2	12	82	0	26.7	Observation [2]
29.3.49	16. F. 139/46	M. D.	12	31.5	17	15.2	0	33.8	Primary pulmonary tuberculosis
4.4.49	17. F. 23/49	S. S.	14	50.8	17	12.3	0	6.3	»
12.4.49	18. G. 118/49	B. S.	13	65.5	15	14.8	0	5.3	Rheumatic fever

[1] Urine at all times quite normal.

[2] Admitted for suspected renal sulfonamide damage. Urine at all times completely normal.

OWN INVESTIGATIONS OF NORMAL INDIVIDUALS

By means of the technical methods described on Page 24, the exchange of radioactive phosphorus has been studied on 101 patients of which Group N_2, according to the classification of the material, consists of 18 children with completely normal kidney, and, in addition, 5 healthy adults.

The phosphate clearance in this group is shown in Tables 7 and 8. The excretion of P^{32} is demonstrated in the Fig. 1. After an intravenous injection, P^{32} can very soon, even after 5 minutes, be found in the urine. The excretion of P^{32} increases, in the course of the first hour, to considerable amounts, as compared to the activity of the blood, and after about 20 minutes the specific activity is higher in the urine than in the blood. This in complete agreement with the results of earlier authors (MÖLLERSTRÖM, GOVAERTS, and others).

TABLE 8

Group N_2 5 normal adults

Date	Initials	Age	Urine	Cl_p	
22. 9. 49.	M.B.	25	0	4,2	Healthy
22. 9. 48.	L.H.	33	0	6,1	»
24. 5. 49.	L.S.	41	0	5,9	»
21. 1. 50.	B.E.	24	0	7,9	»
12. 2. 50.	S.J.	24	0	5,2	»

The relation between the specific activity in the urine and the blood plasma in an individual can be studied by computing the ratio S_u/S_b where the S_u and S_b belong to the same time period (for notation see p. 23) and making a graph of this ratio. To facilitate a comparison between different individuals, it is however, from a statistical point of view, preferable to use the logarithm of this ratio,

$$L = \log S_u/S_b = \log S_u - \log S_b$$

When L is positive, the specific activity is greater in the urine than in the blood, and when L is negative the situation is reversed.

The error of the determination of $\log S_b$ can easily be estimated. We have

$$\log S_b = \log A_b - \log P_b$$

and consequently, from p. 27 and p. 26, for small values of ε_a and ε_p

Fig. 1. Group N2. Means of differences between log spec. activity in urine and in blood = $\overline{L}$.
The shadowed part illustrates the standard deviation in each time period.

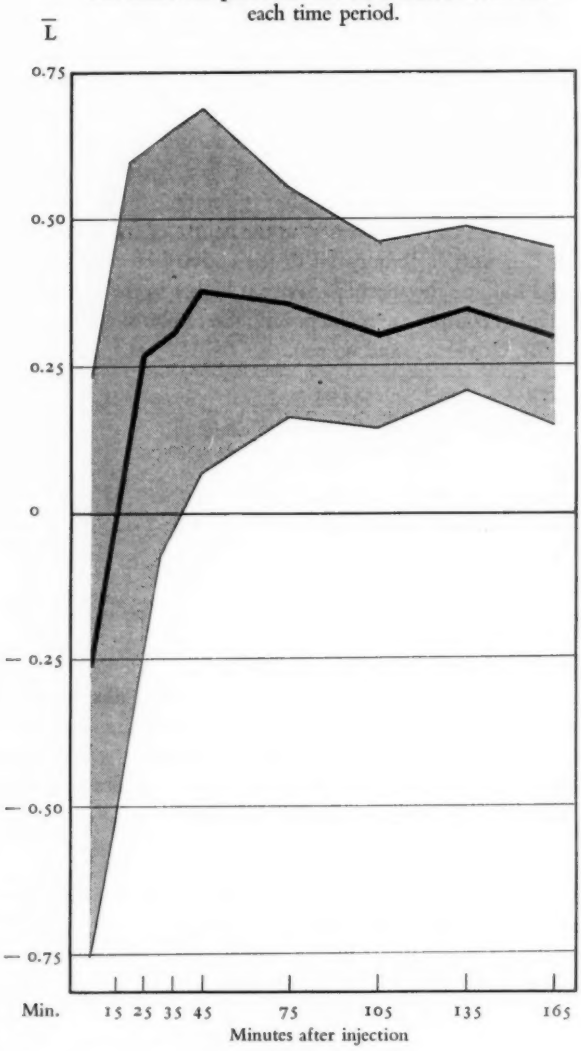
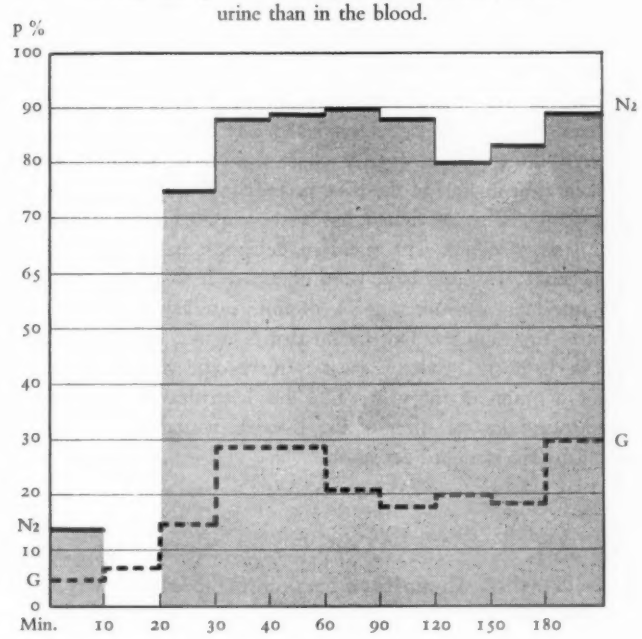


Fig. 2. Groups N2 and G. The percentage of patients in each time period with higher specific activity in the urine than in the blood.



Stand. error of log $S_b \backsim \sqrt{\varepsilon_a^2 + \varepsilon_p^2}$

If e.g. $\varepsilon_a = \varepsilon_p = 5$ %, we find stand. error of log $S_b = 0.07$. Thus we can state that, with 95 % confidence, the true value of log S_b is covered by the limits observed value $\pm$ 0.14. The error in the determination of L probably seldom exceeds 0.30 and is in general less than 0.20.

The value of L has been determined, directly or by interpolation, for each normal patient in as many time periods as possible. In cases where interpolation has not been possible, only the sign of L has been noted, and in several cases no statement regarding L has been possible. Naturally this has been the case in the neighbourhood of the points of intersection of the blood curve and the urine curve.

The results of the calculations have been summarized in Table 9 and Table 10. In Table 9 the percentage of patients with positive L-values has been given for each time period, with at least 7 values. We find from the table that, during the time period 60—85 min., in 90 % of the 23 cases observed L is positive; the specific activity is higher in the urine than in the blood. It is seen that L is positive in more than 75 % of the cases *20 minutes after the time of injection*. The situation is illustrated in Fig. 2 where the percentage numbers have been taken as ordinate and the time periods as abscissa.

In Table 10 the mean value $\bar{L}$ has been computed for each time period with at least 3 values. The standard deviation has been determined when at least 5 L-values have been obtained. It is seen from the table that $\bar{L}$ amounts to about 0.30 in all time intervals belonging to the period 30—175 minutes. This means that $S_u/S_b \sim 2$, so that the specific activity in the urine is twice as great as the specific activity in the blood. In Fig. 1 a graph of the values of $\bar{L}$ has been drawn. The shadowed part illustrates the variation of the L-values round their mean as represented by the standard deviation.

TABLE 9

Group G and N_2. Comparison between the specific activity in urine and blood. p = percentage of cases in each time period with greater specific activity in urine than in blood. n = number of cases.

Periods in minutes	G		N_2	
	p %	n	p %	n
5—10	5	(20)	14	(14)
10—15	7	(14)	—	(6)
20—25	15	(13)	75	(8)
30—35	29	(14)	88	(17)
40—55	29	(14)	89	(18)
60—85	21	(19)	90	(21)
90—115	18	(17)	88	(17)
120—145	20	(20)	80	(15)
150—175	19	(16)	83	(12)
180—205	30	(10)	89	(9)

TABLE 10

Group G and Group N2. Differences between log specific activity in urine and blood.

	Group G			*Group N2*			
Time periods in minutes	$\bar{L}$	s	n	$\bar{L}$	s	n	Diff. between $\bar{L}$-values
0—5	—0.50	0.28	6	—0.26	0.99	5	0.24
10—15	—0.22	0.62	5				
30—35	—0.59	0.55	7	0.30	0.69	11	0.89
40—55	—0.20	0.24	9	0.30	0.62	11	0.50
60—85	—0.07	0.42	17	0.37	0.39	15	0.44
90—115	—0.36	0.34	11	0.31	0.32	15	0.67
120—145	—0.25	0.66	13	0.35	0.28	11	0.60
150—175	—0.52	0.57	11	0.30	0.30	8	0.82

$\bar{L}$ = means of differences in each group and time period.

s = standard deviation of differences.

n = number of differences.

Last column = difference between $\bar{L}$ in Group N_2 and $\bar{L}$ in Group G.

DISCUSSION

The finding that the S_u is higher than S_b has been the subject of a keen discussion. A conceivable explanation may be found in the turnover of P^{32} in the erythrocytes or some other phosphate fraction in the plasma. A turnover in the erythrocytes should, however, be without any significance, at any rate for a time immediately after an injection, as the amount of orthophosphate in the erythrocyte is insignificant. In order to avoid the first alternative, it is, nevertheless necessary to separate the blood cells immediately from plasma by centrifugation. The entire plasma count is found in the acid-soluble portion. The phopholipids and the phosphoproteins are precipitated with the trichloracetic acid.

There must be another explanation. Immediately after the intravenous injection, the new-introduced phosphate ions consist exclusively of diffusible, dissociated orthophosphate ions. They are rapidly excreted with the urine and almost at once an equilibrium between the plasma orthophosphate and the urinary orthophosphate is achieved. If no

regard need be paid to the possibility of some urine being retained in the uropoietic system, the specific activity of orthophosphate of the urine is exactly the same as that of the plasma.

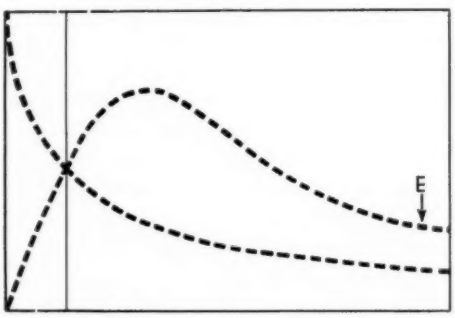
Shortly after the injection, it seems, however, that another system of equilibrium exists between the plasma phosphates, viz.

Plasmaorthophosphate

$$P_u \text{ (ortho)} \underset{\text{rapid reaction}}{\rightleftarrows} P_b \text{ (ortho)} \underset{\text{slow reaction}}{\rightleftarrows} P_x$$

In the left of these two systems ($P_u \rightleftarrows P_b$) the ion exchange is very rapid, in the right it is considerably slower. P_x is not orthophosphate, though analytically behaving like it, and by its presence it implies a dilution of the activity of the plasma. Graphically, the excretion might be demonstrated as in Fig. 3. The fact that the S_u curve crosses the S_b curve, then proceeding above it and gradually reaching an equilibrium, at E, signifies that the ion exchange between P_x and P_b has reached an equilibrium. Thus no further dilution of the specific activity takes place.

Fig. 3.



This argumentation is, from beginning to end, based on a supposed exchange equilibrium between the excreted phosphate and the phosphate compounds of the kidney itself (see discussion and Fig. p. 59).

So far it remains an open question whether this P_x consists of phosphoproteins or phospholipids. From the point of view of the practical results of the present investigation, this question is of no significance.

As mentioned, GOVAERTS regarded the elevated urine isotope ratio as a criterion of the presence of a non-filtrable plasma fraction, in the discussion above called P_x. There is a great deal that speaks in favour of GOVAERTS' theory, but he has hardly produced any final proof. GOVAERTS found that the specific activity of calcium is equal in blood and urine in dogs. This other fraction can, therefore, scarcely be calcium phosphate. He presupposes some labile phosphate compound, slowly synthesized through the influence of an enzyme. FRIEDLÄNDER and WILDE have tried to exclude labile phosphate from their phosphate determinations in the plasma by rapidly alkalizing the TCA extract in the presence of magnesium. The specific activity in the magnesium precipitation is exactly the same as the specific activity, measured directly on the TCA extract.

CHAPTER VI

The renal excretion of P^{32} in pathological conditions

Groups G, N_2K, and F in the present material, include patients with a proceeding renal disease with various stages of functional disturbance. Group G and, to a certain extent Group F, include children with an acute glomerulonephritis in a very early phase. Clinical data will be found in the case histories on page 90 and in Table 11, 12, and 13 respectively.

Group G. The two different principal types of onset are represented. Some show an evidently acute onset with a macroscopic hematuria. In other instances, the onset is more stealthy, though the course of the disease reveals an acute glomerulonephritis. All these cases had an albuminuria. The sediment varied, but was pathologic in 19 cases, *i. e.* it contained according to ADDIS' criteria an increased number of erythrocytes and, or, casts (denoted in the tables with ER and C respectively). Fifteen children had increased non protein nitrogen. The blood pressure was not in any instance conspicuously elevated, according to BROCA's standards but some elevation occurred in at least 8 cases. Two children had quite marked edema, but several others had according to statements in their anamneses, some edema. Concentration and dilution tests were performed in most of the cases but no clearance tests other than those specifically reported.

The sedimentation rate was increased in all the cases. Slight anemia (Hb values < 10.8 gm %) occurred in 5 cases.

The diagnosis of acute glomerulonephritis is questionable in 3 cases (See Case reports p. 90)

Case 49 concerns a boy with a suspected syndroma Banti. He had earlier manifested hepato-splenomegalia without any signs of decreased

TABLE 11

Group G. 20 cases of acute glomerulonephritis

Date	No. of case	Initials	Age in years	Weight in kg	ESR in mm per hr	Blood		Edema	Blood pressure	Urine			NPN in mg %	Clp	Diagnosis
						Hb in g %	RBC			Proteinuria	Sediment	Spec. gravity			
29.1.47	44. F. 697/46	E. L.	7	22.2	20	10.4	3.900	0	95/80	+	ER	1.023	40	4.1	Acute glomerulonephritis
1.2.47	45. G. 46/47	H. S.	6	20.0	65	10.2	4.200	0	90/	+	ERC	1.014	44	4.9	»
17.2.47	46. F. 111/47	M. N.	10	30.0	41	—	—	+	145/100	++	ERC	1.017	196	0.7	»
29.4.47	47. F. 282/47	G. H.	5	18.4	45	10.7	4.950	0	110/70	+	ER	1.012	34	2.1	»
15.6.47	48. G. 439/47	L. K.	9	30.3	25	11.9	4.600	0	120/80	+	ER	1.018	46	2.9	»
19.11.47	49. G. 692/47	R. A.	3	15.7	40	9.8	3.960	0	100/65	+	ER	1.010	41	3.2	» [1]
12.1.48	50. G. 203/48	L. E. J.	10	31.1	16	10.3	4.000	0	135/110	+	ERC	1.003	50	3.4	»
11.2.48	51. G. 110/48	K. E. B.	7	19	41	12.1	4.000	0	105/60	+	ER	1.005	44	4.1	»
9.2.49	52. F. 45/49	M. S.	9	23.8	15	14.5	3.830	0	110/60	+	ER	1.024	37	2.2	»
22.2.49	53. G. 136/49	L. W.	9	28.4	47	12.8	4.570	+	125/80	+	ER	1.009	102	2.4	»
20.3.49	54. G. 634/49	K. S.	4	18.9	10	12.5	4.32	0	90/70	+	ER	1.016	27	2.1	» [2]
5.4.49	55. F. 212/49	E. L.	11	26.4	63	12	3.640	0	115/60	++	ERC	1.046	36	0.9	»
25.4.49	56. G. 280/49	C. H. G.	2	15.3	15	12.6	3.640	0	80/60	+	0	1.024	33	7.8	»
26.7.49	57. G. 435/49	L. S.	6	16.8	42	12.9	4.820	0	110/80	+	ER	1.013	40	2.6	»
29.7.49	58. F. 389/49	L. S.	3 1/2	15.9	15	11.6	5.050	0	130/85	+	ER	1.015	40	2.8	»
20.11.49	59. F. 765/49	U. P.	9 1/2	42.4	31	12.9	4.260	0	120/70	+	ER	1.018	36	8.2	»
10.12.49	60. F. 687/49	A. H.	10	48	16	12.4	4.270	0	135/80	+	ER	1.016	24.3	3.8	»
28.12.49	61. F. 752/49	E. H.	10	37	45	11.2	4.050	0	125/90	+	ER	1.012	33	1.8	»
17.2.50	62. F. 109/50	K. S.	6	27	12	12.7	4.660	0	90/80	+	ER	1.008	40	1.3	»
16.4.50	63. F. 342/50	C. S.	8	28.2	29	12.4	4.800	0	115/65	++	ER	1.011	38	6.8	»

[1]) +Hepato-splenomegaly. [2]) (Nephropathia chron.?)

TABLE 12

Groupe N_2K. 8 cases of acute glomerulonephritis

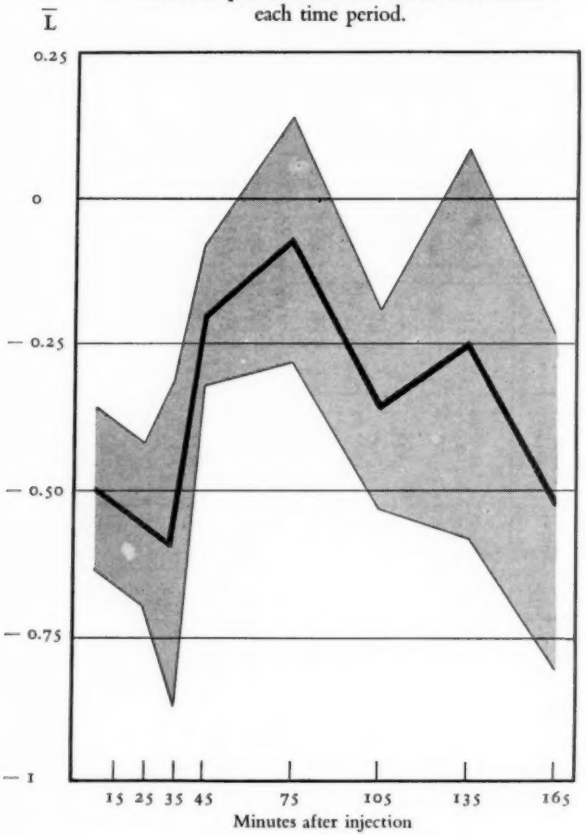
Date	No. of case	Initials	Age in years	Weight in kg	ESR in mm per hr	Blood		Edema	Blood pressure	Urine			NPN in mg %	Cl_p	Diagnosis
						Hb in g %	RBC			Proteinuria	Sediment	Spec. gravity			
31.1.47	71. G. 94/47	K. P.	9	20.9	32	10.1	3.7	0	115/50	—	ER	1.018	54	10.9	Acute glomerulonephritis
31.1.47	72. F. 64/47	G. S.	5	20	18	12.2	4.4	0	90	—	0	1.024	35	6.2	»
1.2.47	73. G. 65/47	Å. B.	5	19.3	60	9.4	4.6	0	125/80	—	ER	1.010	37	10.7	»
21.2.47	74. G. 121/47	K. K.	8	25.8	50	9.4	3.6	0	115/70	—	ER	1.017	51	7.4	»
11.3.47	75. G. 213/47	J. M.	11	33.1	25	12.6	4.5	0	125/75	—	ER	1.017	50	12.1	»
3.6.47	76. G. 145/47	L. Å.	4	17.4	14	13.4	4.4	0	110/90	—	ER	1.015	43	6.7	»
16.6.47	77. F. 355/47	M. A.	5	17.3	45	12	4.2	0	100/85	—	0	1.023	39	8.8	»
16.6.47	78. G. 452/47	I. S.	9	31.2	9	12.9	4.8	0	95/70	—	0	1.024	33	6.0	Status post nephritid

TABLE 13

Groupe F. 7 cases of acute glomerulonephritis

Date	No. of case	Initials	Age in years	Weight in kg	ESR in mm per hr	Blood		Edema	Blood pressure	Urine			NPN in mg %	Cl_p	Diagnosis
						Hb in g %	RBC			Proteinuria	Sediment	Spec. gravity			
17.2.47	64. F. 168/47	A. Å.	10	28.7	32	11	4.2	0	149/90	+	ER	1.018	46	0.57	Acute glomerulonephritis
19.3.47	»	»	10	27.4	27	12.2		0	80	+	ER	1.020	34	4.7	
21.5.47	»	»	10	31.2	15	13.2		0	110/60	+	0	1.023	40	1.7	
19.3.47	65. G. 238/47	H. J.	14	42.8	60	10.6	3.5	0	120/70	+	ER	1.007	29	1.7	»
14.4.47	»	»	14	35	38	13		0	90	(+)	0	1.010	33	3.8	
20.3.47	66. G. 162/47	L. I. B.	10	39.2	16	12.4		0	110/70	+	ER	1.005	35	0.6	»
9.4.47	»	»	10	39	19	11.3	4.4	0	105/65	+	0	1.022	57	2.2	
30.4.47	67. F. 283/47	M. A.	7	44.3	17	11.5	4.3	+	145/100	++	ERC	1.030	91	1.0	»
3.6.47	»	»	7	42.5	55	11.9		+	170/115	++	ERC	1.012	196	0.09	
24.9.49	68. F. 523/49	A. E.	4	17.2	75	9.1	2.9	(+)	110/65	+++	ER	1.008	29	1.9	»
22.10.49	»	»	4	18.2	32	11.3	3.5	0	115/85	+	0	1.023	40	7.0	
1.2.50	69. 135/50	B. W.	10	40.8	15	10.1	3.6	0	120/80	+	ER	1.015	31	0.27	»
3.3.50	»	»	10	41.7	30	9.6	3.4	0	125/80	+	ER	1.012	36	0.8	
22.3.50	»	»	10	41.3	16	9.8	3.5	0	125/80	—	ER	1.014	34	1.1	
6.3.50	70. 1473/50	K. B.	5	17.8	64	10.1	4.0	+	115/65	+	ER	1.010	48	1.2	»
24.3.50	»	»	5	19.4	32	9.2	3.6	0	110/65	—	0	1.012	32	2.9	

Fig. 4. Group G. Means of differences between log spec. activity in urine and blood = $\overline{L}$.
The shadowed part illustrates the standard deviation in each time period.



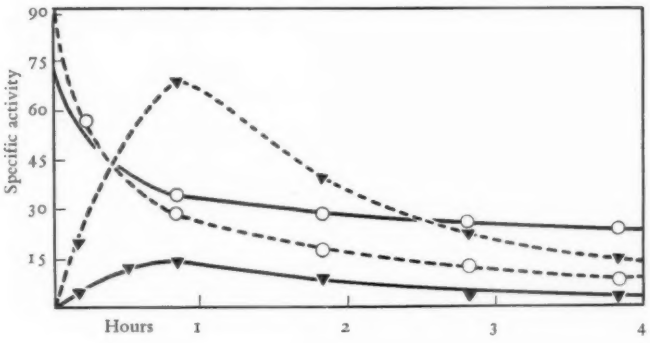
liverfunction. In this particular case, it is perhaps difficult to decide whether the reduced disturbance to the renal function is due to the intercurrent nephritis or to some disturbance in the phosphate metabolism in connection with the enlargement of liver and spleen.

Case 56 concerns a boy who had an albuminuria for the past 7 months. Apart from this, no clinical symptoms of nephritis. Later controls showed

Fig. 5. Case 70. 1473/50 K. B. 5 years. Acute glomerulonephritis. Comparison between the S_u and S_b at two different dates, between which the clinical symptoms of the glomerulonephritis have disappeared.

——— = 6.3.50 o = S_b

..... = 24.3.50 ▼ = S_u



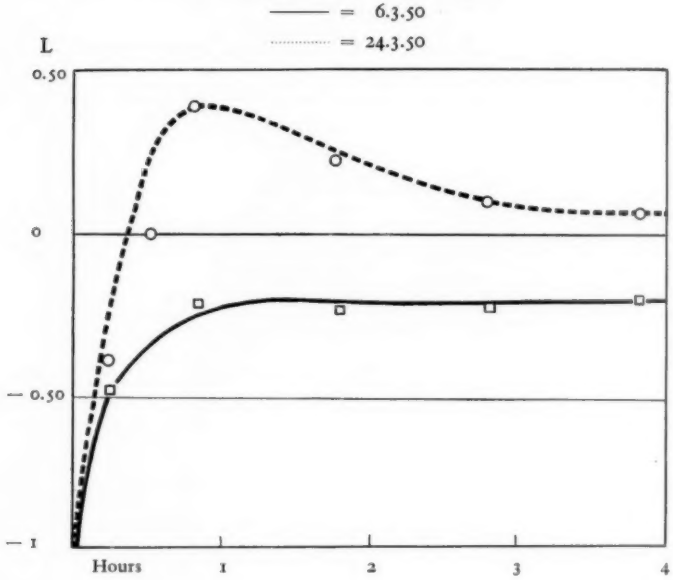
continued albumin in the urine. Otherwise he looked quite healthy. There is no doubt that the renal function is reduced. The possibility of a malformation of the urinary duct system has been considered.

Case 62 concerns a girl, who after two acute infections, had previously had a nephritis and was now subjected to renal irritation a third time in connection with an infection. The diagnosis of orthostatism was dicussed but everything indicates a recurrent, possibly subchronic form of nephritis. Later no relapses.

In two cases, 54 and 63, the course was of long duration and the diseases assumed a subchronic or chronic form. As regards the cases observed in Group F, the tests with P^{32} show a marked change to *increased* or normal excretion of P^{32}, parallel with an improvement of the clinical symptoms, in all the cases but one, *viz*, 67. The course was pronouncedly malignant and led to death in uremia. In this instance, the phosphate clearance was exceedingly low. In the other cases the increase of Cl_p was also evident from one examination to the other.

In Group G, the excretion of P^{32} will, as an average, be found to digress from that of normal children. The curve for S_u lies below that

Fig. 6. Case 70. 1473/50 K. B. 5 years. Acute glomerulonephritis. Difference between log spec. activity in urine and blood (=L) at two different dates. See also fig. 4.

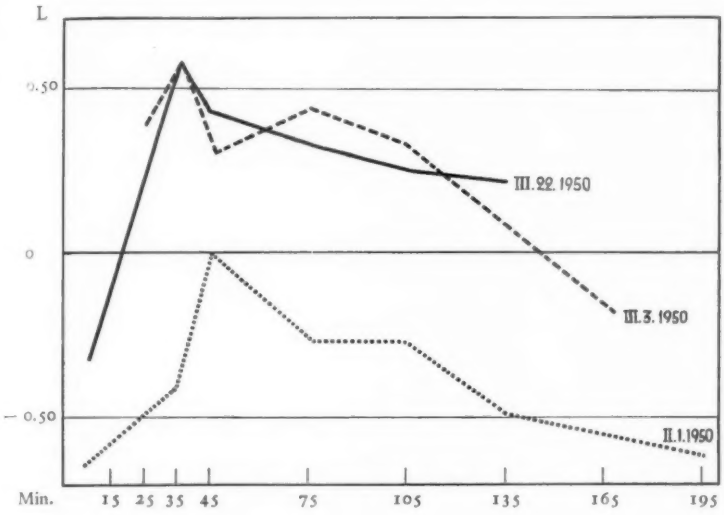


of S_b (see fig. 4). The phosphate clearances (Table 11) were, throughout, low values. The variations in the difference between S_u and S_b may, of course, apart from other sources of error, be dependent upon the degree of the renal damage. This will emerge from the cases in Group F where the course of the disease has been studied by several serial examinations. This is exemplified in the fig. 5, 6 and 7.

From the Tables 9 and 10, as well as from Fig. 2, the $\overline{L}$-values in the N_2 group will be seen to exceed considerably those of the G group. In order to determine if this difference between the two groups may be ascribable to chance fluctuations, the statistical comparison described below has been applied. An account of this statistical method will be found in a series of papers by WILCOXON (1945, 1947).

The value of L was determined as accurately as possible for each patient in the two groups in the neighbourhood of the 60 minutes'

Fig. 7. Case 69. 135/50 B. W. 10 years. Acute glomerulonephritis. Difference between log spec. activity in urine and blood (=L) at three different dates. At the first examination, on Febr. 1 st, the decreased renal function was obvious.



point. If no value could be obtained from an interval of the 60—85 minutes, one of 40—55 minutes was chosen, and if the determination of L failed even in that instance, because of lack of observations, a period of 90—115 minutes was adopted. The L-values from the two groups were arranged in increasing order in one single sequence and denoted by N and G according to whether they belonged to the N_2- or the G -group. The following sequence was then obtained:

Rank number....	1	2	3	4	5	6	7
Category.....	G	G	G	N	G	G	N
L.....	—1.09	—0.51	—0.48	—0.44	—0.39	—0.38	—0.37
Rank number....	8	9	10	11	12	13	14
Category.....	G	G	G	G	G	G	G
L.....	—0.36	—0.35	—0.32	—0.32	—0.31	—0.27	—0.21

Rank number....	15	16	17	18	19	20	
Category.....	G	G	G	G	G	G	
L.....	−0.14	−0.13	−0.11	−0.09	−0.04	−0.02	
Rank number....	21	22	23	24	25	26	27
Category.....	N	N	G	N	N	N	N
L.....	+0.02	+0.03	+0.06	+0.06	+0.11	+0.16	+0.18
Rank number....	28	29	30	31	32	33	34
Category.....	N	N	N	N	N	N	N
L.....	+0.20	+0.22	+0.22	+0.29	+0.34	+0.35	+0.40
Rank number....	35	36	37	38	39	40	41
Category.....	N	N	G	G	N	N	N
L.....	+0.49	+0.51	+0.54	+0.56	+0.63	+0.73	+0.81
Rank number....	42	43	44	45			
Category.....	N	N	N	G			
L.....	+0.88	+0.93	+1.00	+1.12			

Most of the G-values are seen to fall in the first half of the sequence, most of the N-values in the second half. The sum of the rank numbers of the G-values is 342. If no difference existed between the G-values and the N-values, *i.e.* if all permutations of the G- and N-values were equally likely, this sum should, with 99.9 per cent certainty fall between the limits ~~145—506~~ 506 − 145. From this one must conclude that the G- and N-values, on a significance level of 99.9 per cent, belong to different populations.

The 8 cases in Group N_2K (see table 12) represent acute glomerulonephritis in the healing stages. In all of them, the albumin had disappeared from the urine, while pathologic sediment was still present in 5 cases, and increased nonprotein nitrogen in another 5. The blood pressure values lie within normal limits. They have all healed completely. The excretion curves resembled those in normal cases (Fig. 8 and 9 Tables 14 and 15) and the values of Cl_p lie within 3.7 and 10.9.

When Groups G and N_2K are compared, the essential difference is, apparently, the presence of albumin in G and its absence in N_2K. As to the various cardinal symptoms in renal damage, *viz*, proteinuria, pathologic sediment, increased non protein nitrogen and hypertension, proteinuria seems to be the only one that can be correlated to a reduced

Fig. 8. Group N2K. Means of differences between log spec. activity in urine and in blood = $\overline{L}$.
The shadowed part illustrates the standard deviation in each time period.

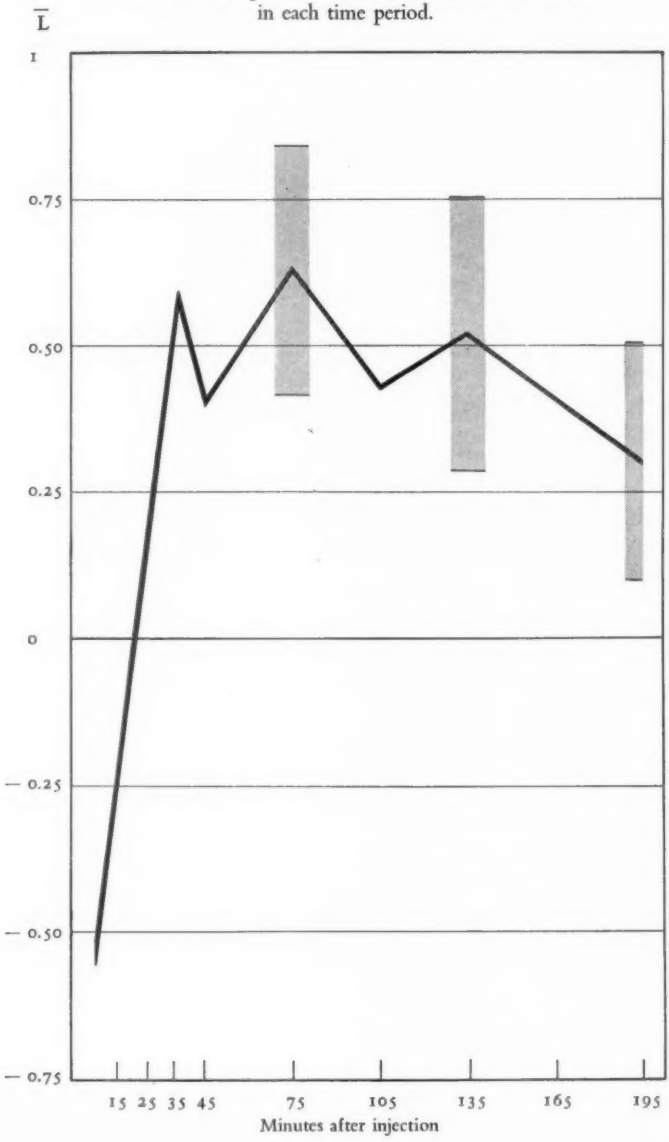


TABLE 14

Group N_2 K. Comparison between spec. act. in urine and blood. p = percentage of cases in each time period with greater spec. act. in urine than in blood. n = number of cases.

Periods in minutes	p %	n
5—10	18	(11)
10—15	36	(11)
20—25	71	(7)
30—35	88	(8)
40—55	100	(7)
60—85	100	(12)
90—115	91	(11)
120—145	90	(10)
150—175	90	(10)
180—205	75	(12)

TABLE 15

Group N_2K. Differences between log specific activity in urine and blood.

Time periods in minutes	$\bar{L}$	s	n
60—85	0.63	0.42	10
120—145	0.52	0.46	10
180—205	0.30	0.40	10

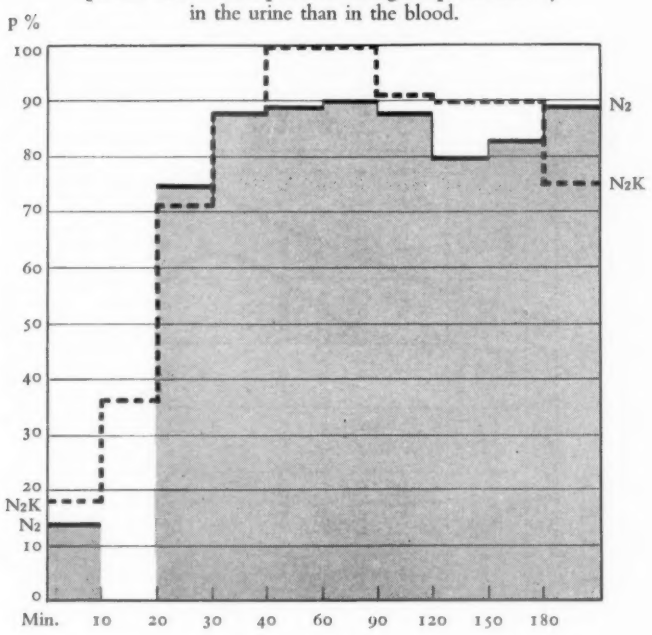
$\bar{L}$ = means of differences in each group and time period.
s = standard deviation of differences.
n = number of differences.

excretion of P^{32}. The presence of albumin was the symptom according to which the division into groups took place.

Group C was finally made to include a few cases that could not be ascribed to the others, in which symptoms of renal damage or pathological constituents in the urine occurred. (Table 16.)

Case 79 concerns a boy, aged 2, with typical symptoms of chronic nephritis (See the Case history, page 101). The excretion curve is illustrated in Fig. 10. The curve seems not to differ from that in the acute cases of glomerulonephritis.

Fig. 9. Groups N_2 and N_2K. The percentage of patients in each time period with higher specific activity in the urine than in the blood.



The cases 80—82 are typical nephroses (Case reports, p. 102). In spite of an considerable albumin excretion, the renal function does not seem to be reduced, not at any rate as far as the excretion of phosphate is concerned. This seems, however, to conform to the view that a nephrosis is not a renal disease but a general disturbance of the albumin metabolism of the organism. As for the individual excretion curves see Fig. 11, 12 and 13.

Case 83 concerns a boy, aged 2, with a D-vitamin resistent rachitis. The onset was at the age of 1 year. He had a pronounced hypophosphatemia hypocalcemia, high phosphatese value and marked rachitic skeletal changes. During the florid rachitis, the excretion of phosphorus in the urine was abnormally abundant with a high Cl_p. Also S_u/S_b was increased and remained thus for a longer time than usual (see Fig. 14).

TABLE 16

Group C

Date	No. of case	Initials	Age in years	Weight in kg	ESR in mm/hr	Blood		Edema	Blood pressure	Urine			NPN in mg %	Cl_p	Diagnosis and remarks
						Hb in g %	RBC			Proteinuria	Sediment	Spec. gravity			
23.8.48	79. G. 605/48	D.W.	1.5	10.2	28	9.5	3.4	—	115/80	+	0	1.009	45	0.9	Chronic glomerulonephritis
16.1.50	80. G. 684/49	B. K.	4.5	23.8	68	8	2.9	++	105/70	++	0	1.013	85	3.4	Nephrosis
24.1.50	81. G. 50/50	K. E.	4.5	13.5	56	11.8	4.7	+	85/75	++	0	1.012	26	4.5	Nephrosis. Malformatio
3.2.49	82. G. 76/49	L. H.	5	25.2	130	12.3	4.5	++	95/70	+	0	1.012	26	6.1	Nephrosis
17.1.50	83. G. 30/50	A. C.	2	10.2	7	10.9	3.9	—	—	—	0	1.013	—	0.7	Rickets, resistent to D-vitamin
9.2.50	83. G. 30/50	A. C.	2	10.3	5	9.8	3.6	—	—	—	0	—	20	1.2	Ca P
3.3.50	83. G. 30/50	A. C.	2	10.8	6	11.2	4.1	—	90/70	—	0	1.014	20	15.2	17.1.50 9.2 mg% 3.9 mg%
															9.2.50 10.8 » 6.7 »
															3.3.50 11.2 » 7.8 »

Fig. 10. Case 79. G. 605/48 D. W. 1.5 years.
Chronic glomerulonephritis.
○ = S_b
▼ = S_u

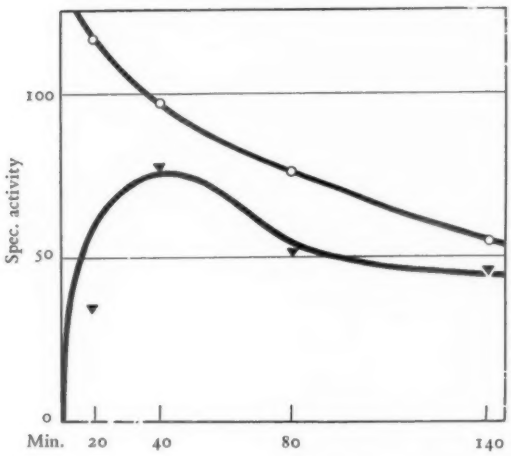


Fig. 11. Case 80. G. 684/49 B. K. 4.5 years.
Nephrosis.
○ = S_b
▼ = S_u

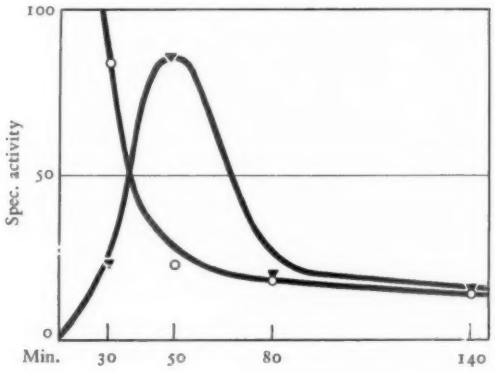
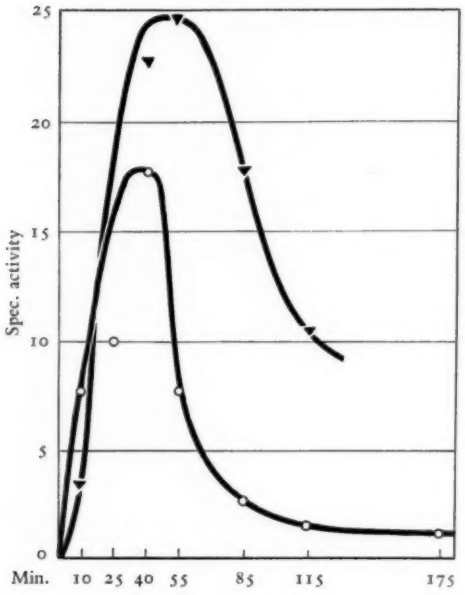


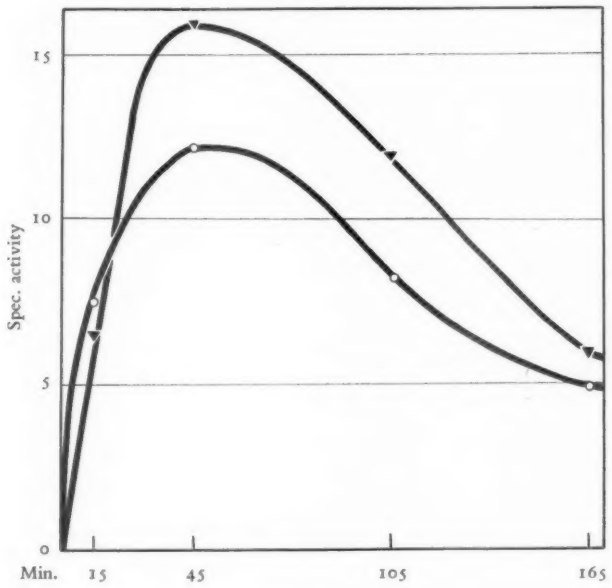
Fig. 12. Case 81. G. 50/50 K. E. 4.5 years.
Nephrosis.
○ = S_b
▼ = S_u



It seemed as though the ion exchange in the mechanism $P_b \rightleftarrows P_x$ was further delayed. When the rachitis had healed, the P-excretion through the urine was normalized.

I have already pointed out the rôle (p. 14) of the kidneys in the phosphate metabolism of the body. Clinical studies of refractory cases of rachitis have confirmed HARRISON and HARRISON's conception that the D-vitamin influences the re-absorption of organic P through the renal tubuli, possibly also that the D-vitamin reduces the excretion through the glomeruli and thereby increases P in the plasma (ROBINSON and NELSON). According to ALBRIGHT, the D-vitamin should, on the other hand, accelerate the excretion of P in the urine. An increased excretion of P through the urine in cases of resistent rachitis has been demonstrated

Fig. 13. Case 82. G. 70/49 L. H. 5 years.
Nephrosis.
○ = S_b
▼ = S_u

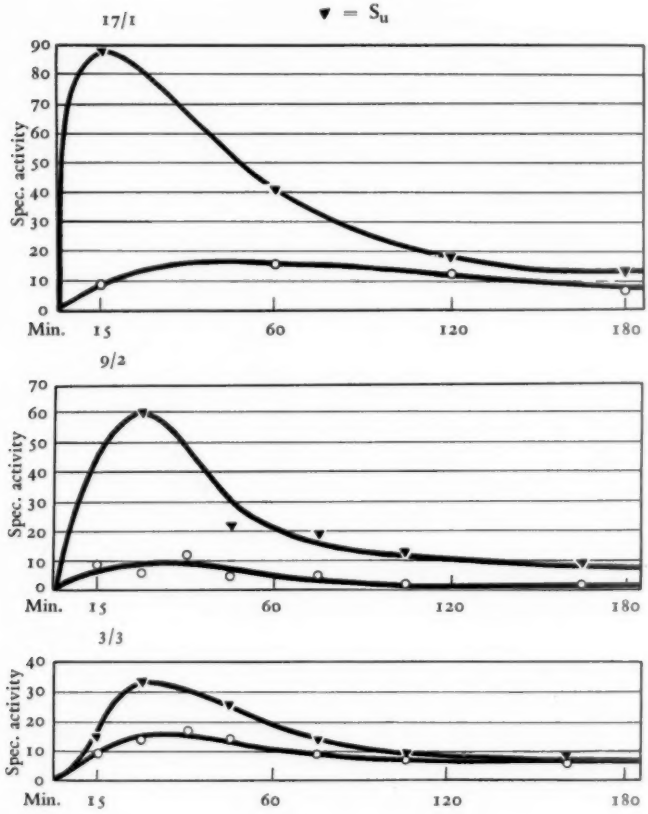


by several investigators (de Toni, Debré, Fanconi, Wallgren). The probability of a disturbed renal function in these cases is borne out by other symptoms of renal damage, such as albuminuria, glycosuria and aminoaciduria.

DISCUSSION

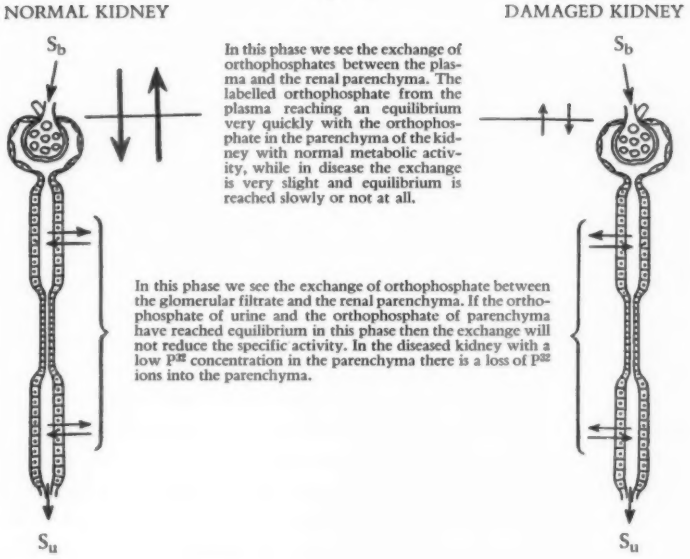
What happens in the morbid kidney? And what is the significance of the reduced excretion of labelled phosphate? Irrespectively of the condition of the glomerules, the specific activity cannot, conceivably, have changed during the passage through the glomerules. No change in the ion dissociation can take place. The primary filtrate has, in some way or other, been mixed with other, unlabelled, phosphate, and this phosphate can hardly come from anywhere else than the kidney itself.

Fig. 14. Case 83. G. 30/50 A. C. 2 years.
Rickets, resistent to D-vitamin. See page 53.



Two possibilities offer themselves, the first, being that a degeneration of tissue, occurs in the morbid kidney with a liberation of phosphate that mixes with the urine. A simple calculation of what then would be used up shows that this would hardly be feasible, since the content of phosphate in the kidneys would not suffice to produce such a distribution, at any rate not in cases of nephritis that recover.

Fig. 15.


NORMAL KIDNEY
DAMAGED KIDNEY
S_b
S_b
In this phase we see the exchange of orthophosphates between the plasma and the renal parenchyma. The labelled orthophosphate from the plasma reaching an equilibrium very quickly with the orthophosphate in the parenchyma of the kidney with normal metabolic activity, while in disease the exchange is very slight and equilibrium is reached slowly or not at all.
In this phase we see the exchange of orthophosphate between the glomerular filtrate and the renal parenchyma. If the orthophosphate of urine and the orthophosphate of parenchyma have reached equilibrium in this phase then the exchange will not reduce the specific activity. In the diseased kidney with a low P^{32} concentration in the parenchyma there is a loss of P^{32} ions into the parenchyma.
S_u
S_u

The second, and more plausible, explanation is that the metabolism in the morbid kidney is being reduced to such an extent that the turnover of P^{32} to the kidney itself decreases.

Mention has already been made of the fact that the phosphate excreted through the renal ducts occupies an exchange equilibrium with the phosphate compounds of the kidney. In a renal damage, or in an immature kidney such as in prematures, these phosphorus compounds (including also the orthophosphate of the kidney) are, for some reason, not found to be in an exchange equilibrium with the orthophosphate of the plasma, as in a healthy kidney.

Because of this, the phosphate is, on its passage through the kidney, diluted with unlabelled phosphate. This is schematically indicated in Fig. 15. Neither the mechanism of this metabolic disturbance, nor its actual nature, are clear. An acidosis in the tissue may, conceivably, constitute the origin. But, on the other hand, a possible acidosis may form another symptom of a reduced metabolism.

CHAPTER VII

The kidney function in prematures

SURVEY OF THE LITERATURE

In a human adult, the glomerular function remains fairly constant, while urinary concentration changes with the reabsorption by the tubules. The filtration is determined from the inulin and creatinine clearances. The creatinine clearance is, however, about 1.3 times as great, resulting, supposedly, from tubular creatinine secretion or a tubular creatinine formation from creatinine phosphoric acid introduced with the blood. In these respects, the renal function of a human adult differs from that of several examined animals. In the rabbit the diuresis depends both on a variation in the filtration and on the reabsorption and the creatinine and inulin clearance are identical.

Apart from the physiologic interest of the problem of the renal function in children of different ages, it is, of course, a matter of the greatest importance to pediatricians to be aware of the excretion capacity of the kidneys of infants and prematures, because of the toxic effects resulting from the accumulations of drugs excreted primarily with the urine.

BARNETT has shown that the clearance of penicillin in children aged 3 to 12 years is much higher than in prematures, whether it be correlated with the body surface or the body weight. (Table 17).

The correlation of the clearance in infants to body surface, body weight, the weight of the kidneys, basal metabolism, age, etc., has not been fully studied. So far, in the literature, most clearance studies have been correlated to the body surface, this being thought to be preferable, in attempting comparisons with adults (MC CANCE, WEST, RUBIN et al.).

It is only during the past 10 years that attention has been directed to the renal function in newborns and prematures. MCCANCE made a

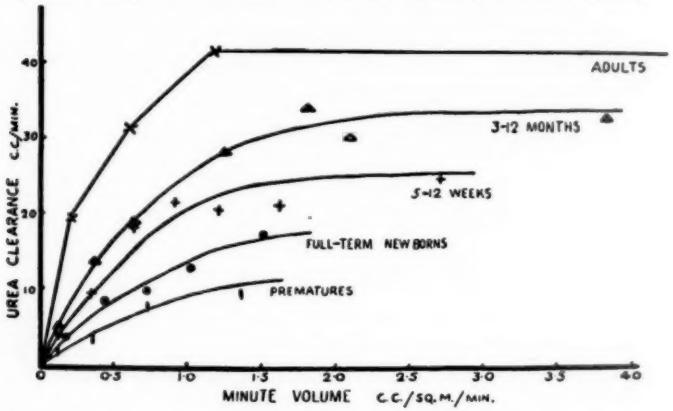
Table 17. Clearance of inulin and penicillin G
(From Barnett Henry L., Kidney function in young infants
Pediatrics Vol. 5, no 2, 1950)

No	Age	WT Kg	HT CM	Mean clearances Ml per min. per 1.73 sq.m Inulin	Penicillin G
			CHILDREN		
12	3—12 yrs	13—46	95—150	127 (93—145)	560 (311—954)
			PREMATURE INFANTS		
4	4—8 days	2.2—2.3	47—47.5	44 (31—53)	90 (72—114)

study of the question of the difficulty in securing satisfactory pyelograms in infants. His investigations convinced him that the difficulty originated in a reduced renal function. DEAN and MCCANCE had noted that the inulin clearance in infants, 2—4 days old, amounted to 16—45 ml/min and the diodrast clearance to 24—125 ml/min, with correction for the body surface. In prematures weighing between 2.156 and 2.470 gm, BARNETT found an inulin clearance of 3—5 ml/min. In full term babies, only a slightly higher clearance was observed, *viz*, 5—7 ml/min. In correlation to the body surface, these values represent about 35—40 per cent of a clearance value of 124 in adults. VESTERDAL and TUDVAD determined the inulin and PAH clearance in infants aged 1—118 days with birth weights of 1.000—3.750 gm. They were able to confirm MCCANCE's and BARNETT's determinations. They found that there was no significant difference in the reducted clearances to be found in newborns, full term infants, or prematures with a birth weight above 1.500 gm, but that it was a still greater reduction of clearances to be noted in prematures below 1.500 gm. Both inulin and PAH clearance rose rapidly in the weeks after birth, though with marked individual variations. They also observed that pain decreased the clearance and that a high diuresis increased the clearance.

At what age will children produce clearance values corresponding to those of adults? WEST, SMITH and CHASIS determined mannitol and PAH clearances in healthy infants aged 1/2—110 weeks. They found

Fig. 16. Comparison of the average urea clearances of adults and of infants at four different ages.
(From Young, W. F. and Mc Cance, R. A., Arch. Dis. Childhood, 1942)



that adult values, with corrections to a body surface of 1.73 sq.m, are obtained somewhere between the 2nd-3rd and the 8th–10th months.

Young and McCance have compared the urea clearances of adults and infants of different ages, (see fig. 16).

Simultaneously with the publication of McCance's and Dean's first investigations, Gruenwald and Popper announced an investigation regarding glomeruli from infant kidneys in which they concluded that, in place of a basement membrane surrounding the capillary tuft in the glomerulus, there was actually a high columnar epithelium. They inferred that the filtration would be impeded by this kind of epithelial membrane.

As far as the tubular function is concerned, reference can, again, be made to the works by McCance and Dean. They noted that the diodrast clearance in infants is low, not in an absolute sense, but relatively, in proportion to the inulin clearance (Homer W. Smith). In all likelihood, the tubular cells are not fully developed at birth, at any rate not sufficiently to excrete diodrast corresponding to adult levels. This explains the difficulty in obtaining filling of the renal pelvis in an infant kidney in performing intravenous pyelograms. An inferior tubular function in infants is also suggested by the forementioned fact that the creatinine

clearance in infants equals the inulin clearance; the significant part of creatinine excretion that takes place through the tubules in adults, is not found in infants.

LEVINE and GORDON observed that when cow's milk, which has a higher content of sodiumchloride than mother's milk, was given to infants, there was a lag in the rate of excretion of the salt. From this, they concluded that the renal function was not fully developed.

In a newborn, the urine is hypotonic or isotonic, which has been thought to be a result of the undeveloped stage of Henle's loop at birth. Before birth, the excretory functions of the foetus arecarried on by the placenta, but the foetal kidney is not entirely functionless. The concentration of urea and uric acid in the *liquor amnii* steadily increases up to the time of delivery and, the urinary bladder of the child contains small amounts of hypotonic acid urine. Total renal secretion is shown radiografically (by KJELLBERG and RUDHE) from and including the 4th—5th foetal month.

PHOSPHATE CLEARANCE

The phosphate clearance in infants is also lower than in adults (MCCANCE). MCCRORY, FORMAN, MCNAMARA and BARNETT found that an increase in the plasma phosphate in newborns, with or without tetany, was due to a reduced glomerular filtration rate. The amount of filtered phosphorus, reabsorbed and excreted, in 7 children with endogenous elevations of plasma phosphorus (8.4—9.6 mg per 100 cc), 4 of whom had a clinically manifest tetany, was compared with findings in normal children. The tubular reabsorption of phosphorus was not increased. Filtered and excreted P was of the same amount in both groups in those cases where the plasma P did not exceed 8 mg%. Since the filtered P is the product of P in plasma and the glomerular filtration rate, it is the latter that must be reduced in children with an elevated plasma P. Injections of parathyroid hormone brought about a prompt increase in the phosphorus excretion simultaneously with a decrease in the reabsorption. The reverse effect was produced when P was decreased in the food.

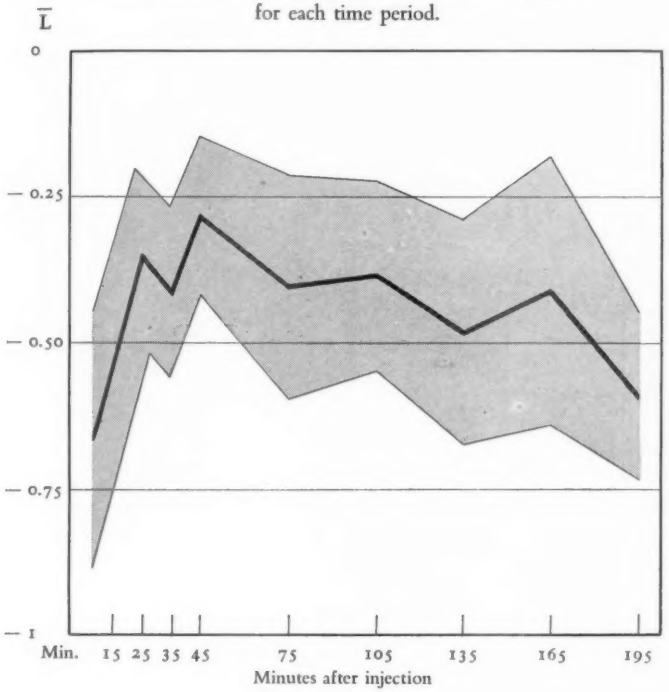
From his investigations of pH, titrable acid, ammonia and phosphate excretion MCCANCE concludes that the urine in infancy must be short of some of the buffer substances that contribute to the titrable acidity

TABLE 18

Group N_1 15 cases of prematures

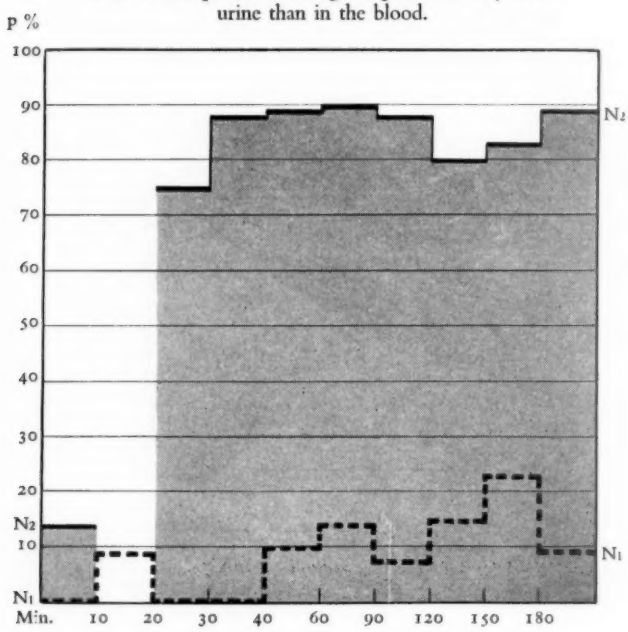
Date	No. of case	Initials	Age in days	Weeks premature	Delivery	Birth weight in gm	Weight when tested	Blood		Urine	Cl_p	Diagnosis
								Hb in g %	RBC			
14.2.49	29. G. 43/49	J.W.	24	4	Twin 2	1.300	1.450	4.6	2.1	Normal	0.8	Twin premature. Congenital debility Anemia. Intracranial hemorrhage.
16.2.49	30. G. 89/49	F. K.	8	11	Normal	1.620	2.350	18.5	16.8	»	1.6	Prematurity
29.5.49	31. G. 319/49	K. P.	24	—	»	2.200	2.240	16.2	4.59	»	0.46	»
30.5.49	32. G. 333/49	B. F.	13	6	Twin 1	2.070	2.320	14.3	4.2	»	0.02	Twin premature
2.6.49	33. G. 371/49	B. O.	7	8	Normal	2.000	1.730	15.5	4.86	»	0.93	Prematurity
18.6.49	34. F. 310/49	E. B.	29	13	»	880	1.400	14.7	3.38	»	0.09	»
22.6.49	35. G. 370/49	N.W.	18	7	»	1.910	2.010	18.6	4.9	»	0.04	»
26.6.49	36. F. 333/49	U. J.	18	6—8	»	1.500	1.700	14.5	3.91	»	1.5	»
30.6.49	37. G. 404/49	N. T.	7	6	»	2.300	2.080	17.3	4.27	»	0.7	»
1.9.49	38. G. 478/49	L. L.	23	13	»	1.020	1.260	8.9	2.34	»	3.9	»
8.9.49	39. F. 475/49	B. N.	3	4	»	1.990	1.890	14.8	4.09	»	0.16	»
9.9.49	40. G. 510/49	O. L.	19	6	»	1.950	1.950	15.6	3.53	»	3.0	»
16.10.49	41. F. 486/50	E. N.	19	2	»	2.400	2.460	12	88?	»	0.9	»
29.10.49	42. F. 552/48	H. L.	26	8	Sectio Cesarea	1.490	1.950	12.1	3.04	»	2.1	» Acute pyelitis
10.11.49	43. F. 19/50	G. B.	28	5	Normal	1.880	1.750	14	3.72	»	1.8	»

Fig. 17. Group N. Means of differences between log spec. activity in urine and blood = $\overline{L}$.
The shadowed part illustrates the standard deviation for each time period.



of adult urines; also infant urine, in fact, contains very little of P. The absence of phosphate in infant urine must constitute a handicap to a child that has an excess of acid to excrete. Consequently, an infant is less well equipped to overcome an acidosis. The production of acidosis in prematures to whom protein milk has been given, described by DARROW and his associates and, then, by HOFFMAN et al, is an example of this deficiency. BARNETT points out that it is, in fact, the limited function of this kidney that provides the physiologic basis for supplying a hypotonic NaCl solution for the repair of dehydration in the young infant.

Fig. 18. Group N2 and N1. The percentage of patients in each time period with higher specific activity in the urine than in the blood.



OBSERVATIONS ON PHOSPHATE CLEARANCE USING P^{32} IN PREMATURES

Determinations of phosphate clearance and P^{32} excretion were performed on a group of 15 prematures aged 3—29 days, with birth weights of 880—2.400 gm and actual weights of 1.260—2.460 gm. The activity of the intraperitoneally injected P^{32} was 2 microcuries per kgm of body weight. The injections were made on an empty stomach. Blood samples were taken at fixed hours and, as far as possible, simultaneously with urine samples. Catheterizations were done with a catheter the size of 10—12. No disturbances were noted from the catheterizations. The diuresis has not been hastened or increased through intake of fluids. Fourteen of the prematures were completely healthy, without any sign

TABLE 19

Group N_1. Comparison between spec. act. in urine and blood. p = percentage of cases in each time period with greater spec. act. in urine than in blood. n = number of cases.

Periods in minutes	p %	n
5—10	0	(9)
10—15	9	(11)
20—25	0	(8)
30—35	0	(8)
40—55	10	(10)
60—85	14	(14)
90—115	7	(15)
120—145	15	(13)
150—175	23	(13)
180—205	9	(11)

TABLE 20

Group N_1. Differences between log specific activity in urine and blood.

Time periods in minutes	$\bar{L}$	s	n
10—15	—0.66	0.44	10
30—35	—0.41	0.29	7
40—55	—0.28	0.27	9
60—85	—0.40	0.39	12
90—115	—0.38	0.32	13
120—145	—0.48	0.38	11
150—175	—0.41	0.46	9
180—205	—0.59	0.28	9

$\bar{L}$ = means of differences n each group and time period.
s = standard deviation of differences.
n = number of differences.

of complications. One premature (J. W., 29. 43/49,) showed symptoms of an intracranial hemorrhage and developed a marked anemia. When the test was performed, his general condition was fairly good, but he has, both before and after the test, been retarded in his growth

and development. The Cl_p in this group was 1.2±0.29. The values are corrected to "Capacitance surface" according to LIND and KARLBERG. (Table 18.)

In all these cases, the specific activity in the urine has proved to be lower than in the blood (Table 19 and 20. Fig. 17 and 18). Thus, the results conform well with those of MCCANCE's and other authors. One must conclude from these figures that both the glomerular and tubular functions are subnormal in the premature.

The conceivable causes of the noteworthy excretion curve of P^{32} are discussed in Chapter IX.

CHAPTER VIII

The renal function in diabetic children

SURVEY OF THE LITERATURE

Among late complications in diabetes, nephropathy no doubt takes the foremost place. From her investigation of 2119 patients, performed during the years 1898—1946, PRISCILLA WHITE draws the conclusion that nephropathy forms the predominating cause of death when the first onset of diabetes dates back to childhood. Only 5 per cent of 250 cases where diabetes set in before the age of 15 years, with a duration of 20 years, were completely free from complications. GRILL has carried out after-examinations of 105 cases of diabetes in which the diagnosis was determined at an age of 20 years, the most recent in 1937, finding albuminuria in 28 per cent with a mortality in nephropathy of 1.9—2.9 per cent. On an average, the onset of the albuminuria is noted 11 and 10 years after the first appearance of the disease, for women and men, respectively. WHITE also mentions the figure of 10 years. As GRILL suggests, it seems that after 10 years attention has to be concentrated on the vascular system and kidneys of diabetics. On a Swedish material, embracing all known cases of diabetes in Dalecarlia, ENGEL had found that 25 per cent had a nephropathy. It largely determined the juvenile diabetic prognosis. It did not appear before 7—8 years after the onset of the disease.

LICHTENSTEIN's (1945) analysis of 169 cases of diabetic children and young patients up to an age of 29 years disclosed no instance of rise in blood pressure or x-ray vascular calcification. This is contrary to WHITE, who states that, in a material of 150 cases, 1 in 6 had arteriosclerosis in his second decade and 1 in 5 in his third. CROOM and SCOTT likewise present more favourable statistics. Among 60 cases who had had their diabetes for 10 years, they noted only 2 with nephropathy. JOHN finds

26 cases of albuminuria in 83 cases, observed for up to 25 years, i.e. 31.3 per cent.

The most dismal statistics are reported by FANCONI from Switzerland. Out of 134 diabetics, 87 of whom were satisfactorily controlled, every one had nephropathy after 16 years, and within 21 years all were dead. He connects this miserable prognosis with the diet which is deficient in proteins and rich in fat. Among the various causes of diabetic nephropathy, the most usual are probably the following ones (HOGEMAN):

Factors connected with metabolic disturbances, *e.g.*, renal changes due to acidosis or coma and "glycogennephrosis".

Infections owing to the generally increased susceptibility of diabetics, the most important being infections of the urinary tract.

Such changes as generally accompany arteriosclerosis, the etiology of which still remains obscure.

As a rule, a diabetic nephropathy will reveal itself as a transient albuminuria, edema and a slight rise in the blood pressure. Gradually, a massive albuminuria, hyperglobulinemia and hypercholesteremia will develop. The final stage produces a syndrome of a malignant nephrosclerosis.

From a patho-anatomic point of view, KIMMELSTIEL and WILSON, have characterized the disease as an inter-capillary glomerulosclerosis. They published their 8 autopsy cases in 1936, describing the disease complex as rare. It should affect only cases of diabetes of more than 40 years duration. According to ROSENBACH, it is noted also in juvenile diabetics.

Recent research regarding the patho-anatomic substratum of diabetic nephropathy has, however, shown that KIMMELSTIEL-WILSON'S intercapillary glomerulosclerosis hardly corresponds to a uniform clinical complex of the type of a diabetic nephropathy. According to ENGEL, the clinical nephropathy in the majority of his cases rather suggests a malignant sclerosis.

Obviously, the disease manifests every degree, from inconsiderable lesions to an extensive degeneration.

Should von BAHR'S (1947) hypothesis, *viz.* that a proliferative retinitis, rubeosis iridis and other vascular lesions occur simultaneously with a diabetic intercapillary glomerulosclerosis, be correct, the diagnosis would be easier and more definite. DOLGER (1946—47) found that 50 per cent of cases with an established retinopathy also disclosed clinical

signs of nephropathy. In his opinion, a nephropathy, of a varying degree of severity, occurs in *all* cases of diabetes of a sufficient duration.

A great many other investigations have been performed in order to ascertain the frequency of a diabetic retinopathy in connection with albuminuria. BESSIÈRE notes a frequency of up to 89 per cent. The occurrence of albuminuria in diabetes is stated very differently by different authors, from 27 per cent (O'DONOGHUE 1931) to 16 per cent (HANUM 1938).

The connection between renal diabetes and reduced renal function has also been the subject of several investigations. It is, however, difficult to draw any definite conclusions from these investigations, since the materials have not been uniform, the clearance methods being multifarious and the investigations were carried out at different stages of treatment.

COMBIER (1934) was the first to investigate the renal function in uncomplicated diabetic cases. He found higher filtration values, determined from creatinine clearance in these cases, than in normal ones, a fact due, in his opinion, to some hypophyseal effect. HOGEMAN has been unable to verify these conclusions. He has studied the renal function in 12 cases of uncomplicated diabetes and in 12 cases of diabetes with nephropathy (albuminuria, pathological urinary sediment, rise in blood pressure and retinopathy) determining the inulin and diodrast clearance and, likewise, in a few cases, the creatinine urea clearance. He arrives at the following conclusions:

1. In cases of uncomplicated diabetes, the renal function does not deviate from the normal.

2. In cases of diabetic nephropathy, a reduction of the renal function is *usually* to be found.

3. These latter cases show the same result of the clearance tests as in malignant hypertension. He is, nevertheless, of the opinion that diabetic nephropathy has a better prognosis than the malignant sclerosis. The filtration factor is high in the latter instance, mostly low in diabetic nephropathy.

4. According to HOGEMAN, this latter fact, together with the more favourable prognosis, suggests a different localization of the renal damage in these two diseases.

HOGEMAN's cases are all adults. The present author has been unable to trace in the literature any systematic investigation of the renal function in diabetic children.

PRESENT INVESTIGATIONS

At Norrtull's Hospital, 30—40 patients are at the time of writing subjected to regular observation. We have tried to perform a thorough investigation of these cases including a comprehensive physical examination. I propose to restrict myself below to, chiefly, the examinations of the kidneys.

Apart from routine tests of albumin, sediment, non-protein nitrogen and blood pressure, the renal function has been tested with inulin and PAH clearances and the excretion of P^{32}. Twentythree of these children, at an age of 6—15 years, have so far been examined. The duration of their diabetes varied from 2 to 13 years. Apart from insulin, mostly consisting of a combined protamine and normal insulin, they have all from the beginning been treated with a free diet.

Clinical symptoms of nephropathy have been discovered in 3 cases with a diabetes duration of 8, 10 and 10 years, respectively. In none of these instances was any hypertension found, but there was a moderate albuminuria and, in addition, in one of the girls, a pathologic sediment.

One girl who has had her diabetes for 7 years, has on two occasions shown traces of albumin. On account of a nystagmus, her eyes have been difficult to examine but, in all likelihood, there is no retinopathy.

Retinopathy was found in 4 cases. In two of these there were no clinical symptoms of renal damage. The third of these cases shows the gravest nephropathy.

Among other symptoms of diabetic complication, mention may be made of the following:

Hypercholesteremia in 3 cases.

Disturbances of the liver function in 2 cases.

Growth disturbance in 1 case.

> (Girl, 9 years old. Diabetes of 3 years' duration. Length 118 cm. Weight 24.8 kg. This patient is alone in having a constant elevation of blood pressure of 135/85).

Lipodystrophy has been noted in 5 cases.

A survey of the clinical symptoms is given in Table 21.

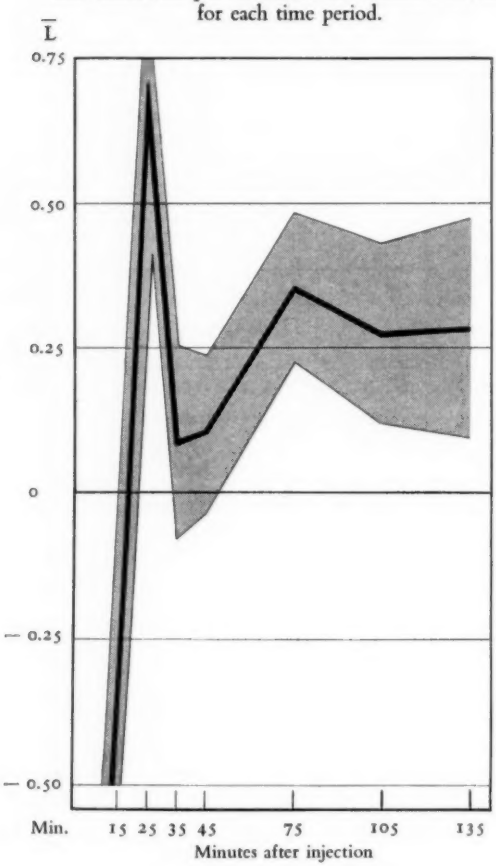
TABLE 21

Group S. 23 cases of Diabetes mellitus

Case	(84) 469/49 BDS, boy	(85) 320/50 IMP, girl	(86) 1130/43 ST, girl	(87) 304/50 GI, girl	(88) 1057/42 MS, girl	(89) 685/50 BB, girl	(90) 555/47 UBI, girl	(91) 271/50 JW, girl	(92) 309/50 BMS, girl	(93) 289/50 SJ, girl	(94) 332/50 BK, girl	(95) 360/50 KB, girl	(96) 620/50 MO, girl	(97) 126/51 TN, boy	(98) 515/44 BB, boy	(99) 749/50 BK, boy	(100) 662/50 VE, girl	(101) 672/50 BB, girl	(102) 799/50 GJ, boy	(103) 293/50 GL, girl	(104) 251/47 GMO, girl	(105) 298/48 LB, boy	(106) 373/43 RJ, boy
Age in years	11	14	12	14	12	15	12	10	10	9	11	14	14	11	9	8	10	13	11	8	11	6	13
Duration of Diabetes	10	8	7	13	10	3	4	2.5	4	3	5	7	2	5	6	3.5	2.5	10	3	3.5	9	3	10
Clinical signs of Nefropathy	+	+	(+)	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Retinopathy	+	—	—	+	—	—	—	—	—	—	—	—	(+)	—	—	—	—	—	—	(+)	—	—	—
Hypertension	—	—	—	—	—	—	—	—	—	+ (135/85)	—	—	—	—	—	—	—	—	—	—	—	—	—
Cl_{IN}	147 *205	72 151	79	91	114	108	115	62	87	106	74	197	151	126	124	166	111	152	140	171	177	190	96
Cl_{PAH}	739 *648	630 742	745	501	548	468	578	480	577	664	449	574	433	558	434	554	863	587	736	—	574	609	819
Cl_p	43.7 *10.5	38.2 10.4	8.0	18.5	27.0	1.8	38.2	25.9	39.9	48.7	44.9	19.4	19.8	18.1	13.8	38.1	17.1	22.6	16.0	34.2	20.9	17.5	10.4
Liver disturbances	—	(+)	—	+	—	—	—	—	—	—	—	—	—	—	+	—	—	—	—	—	—	—	—
Decreased excretion of P^{32}	+	+	+	+	+	+	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—

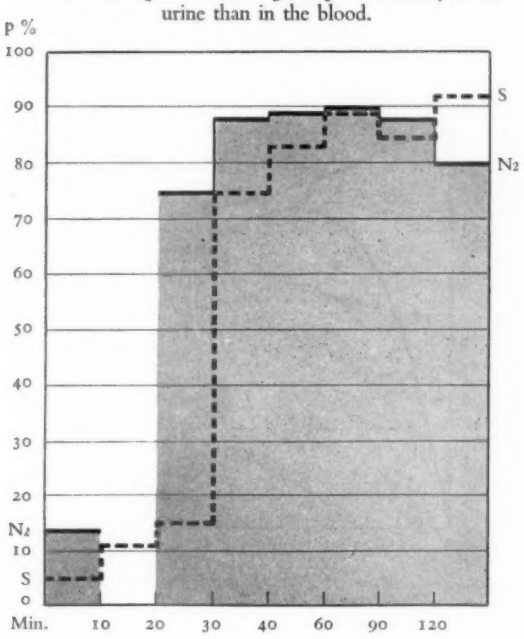
* Two examinations at different dates. See fig. 20 and fig. 21.

Fig. 19. Group S. Means of differences between log spec. activity in urine and in blood = $\overline{L}$. The shadowed part illustrates the standard deviation for each time period.



The patients have been examined on an empty stomach, without having been given their morning insulin (the insulin causes a conspicuous reduction of the urinary phosphorus for the next 6 hours after an injection). Otherwise, they have shown a good tolerance with moderate urinary quantities. The sugar excretion in the urine has not been too

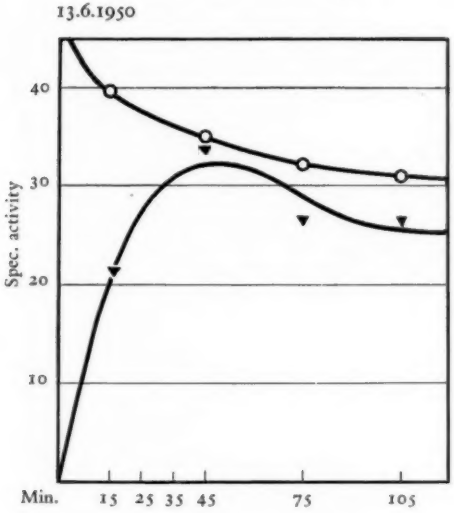
Fig. 20. Groups N2 and S. The percentage of patients in each time period with higher specific activity in the urine than in the blood.



big. Nor have they had any signs of present infection. Simultaneously with the insulin and PAH clearance, the excretion of P^{32} has been performed in the usual manner.

Nineteen of the 23 children were found to have a normal renal function. The other 5 who have been subject to determinations have, without exception, on all occasions proved to have phosphate retention. Three of these 5 have manifested clinical symptoms of nephropathy. The remaining 2, girls aged 12 and 14 years, with a diabetes duration of 10 and 13 years, respectively, have had no usual clinical signs of nephropathy. Both these cases have a relatively poor insulin tolerance and, on several occasions have been admitted to the hospital in a precomatose condition. The elder girl, in addition, shows symptoms of a liver damage. An earlier liver puncture (1944) disclosed signs of a

Fig. 21. Case 84. G. 469/49. B. D. S. 11 years.
Diabetes mellitus + Nephropathy + Retinopathy.
○ = S_b ▼ = S_u



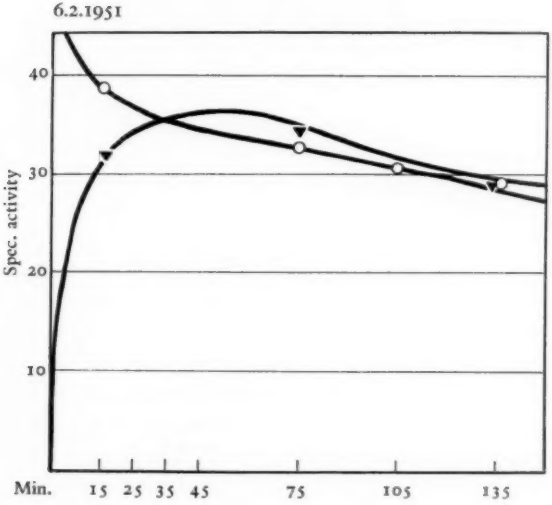
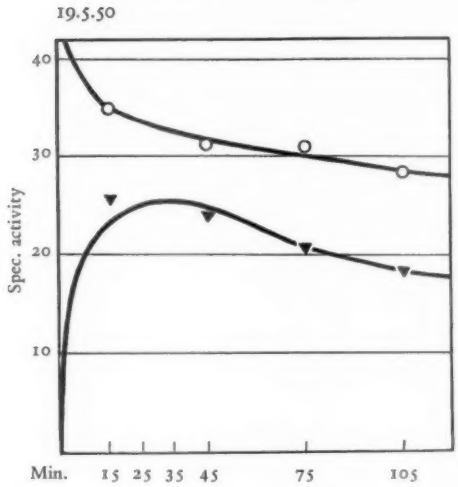


Fig. 22. Case 85. F. 320/50 I. M. P. 14 years.
Diabetes mellitus + Nephropathy.
○ = S_b ▼ = S_u



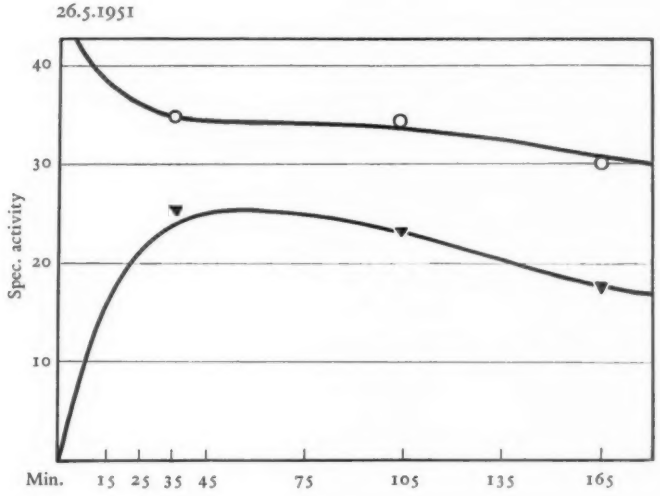
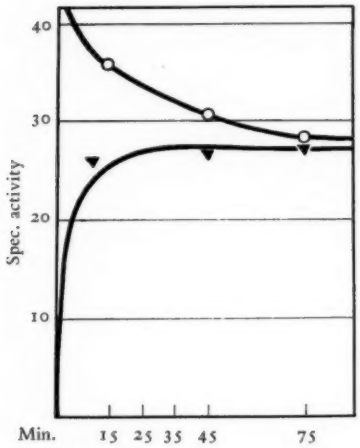


Fig. 23. Case 86. F. 1130/43 S. T. 12 years.
Diabetes mellitus + Transitorial proteinuria.
○ = S_b ▼ = S_u



fairly severe adiposis and glycogen accumulation. In one of the nephropathic cases, creatinine clearance showed a slightly reduced filtration. I have not ventured to draw any definite conclusions from the inulin clearance. The values appear to lie within normal limits. Also the PAH values were found to be within normal limits. It is, in my view, worth noting that the clearance tests now in use do not always answer to a reduction in the renal function, not even when an evident phosphate retention is noted. The results appear to conform to HOGEMAN's on adults. In clinically uncomplicated cases, the renal function does not deviate from the normal and, in cases of diabetic nephropathy, the renal function is obviously *not by necessity* reduced, even though it is supposed to be, *as a rule* reduced. On the other hand, a phosphate retention seems to occur in cases of diabetic nephropathy, and a reduced excretion of P^{32} may, possibly, constitute an initial symptom of diabetic renal damage.

The result of P^{32} test is shown in Tables 22 and 23 and in Fig. 19 and Fig. 20.

Fig. 24. Case 87. F. 304/50 G. I. 14 years.
Diabetes mellitus + Retinopathy.
○ = S_b ▼ = S_u

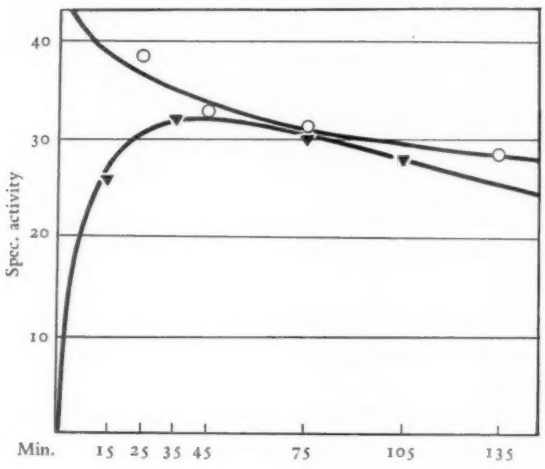


TABLE 22

Group S. Comparison between spec. act. in urine and blood.
p = percentage of cases in each time period with greater spec. act. in urine than in blood. n = number of cases.

Periods in minutes	p %	n
5—10	5	(19)
10—15	11	(18)
20—25	15	(13)
30—35	75	(9)
40—55	83	(18)
60—85	89	(18)
90—115	84	(18)
120—145	92	(12)

Fig. 25. Case 88. F. 1057/42 M. S. 12 years.
Diabetes mellitus.
○ = S_b ▼ = S_u

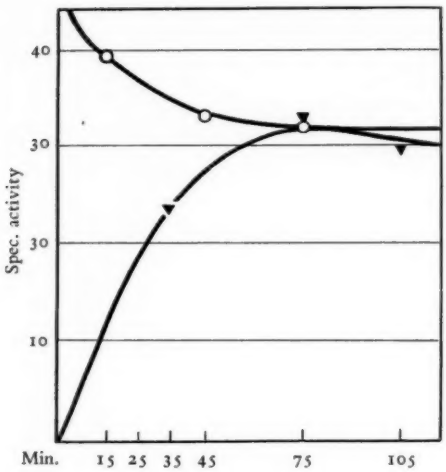


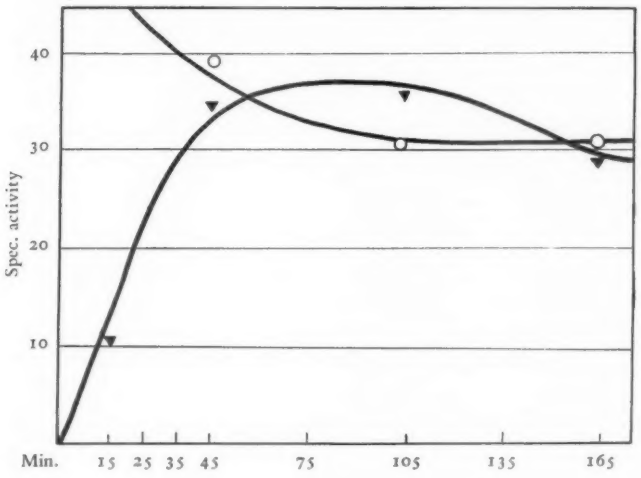
TABLE 23

Group S. Differences between log specific activity in urine and blood.

Time periods in minutes	$\bar{L}$	s	n
10—15	—0.95	0.44	12
30—35	0.08	0.33	6
40—55	0.10	0.28	12
60—85	0.35	0.26	13
90—115	0.27	0.31	17
120—145	0.28	0.38	8

$\bar{L}$ = means of differences in each group and time period.
s = standard deviation of differences.
n = number of differences.

Fig. 26. Case 89. F. 685/50. B. B. 15 years.
Diabetes mellitus.
○ = S_b ▼ = S_u



The Cl_p is remarkably high 24.03±2.35 (Compare with the values of the normal group 9.8±1.6). In the cases of diabetic nephropathy the corresponding value of Cl_p is 18.3±4.3, thus a rather high value.

All the diabetic children with a pathological P^{32} excretion are illustrated in individual graphs (Fig. 21—25). Fig. 26 illustrates the excretion of P^{32} in a "normal" case (89, 685/50), occasionally in a state of acidosis. This girl had no signs of nephropathy, but this actual examination was carried out when she had been admitted in a precoma with marked acidosis. Two other examinations of this girl showed completely normal P^{32} excretion.

For discussion of this group see Chapter IX.

CHAPTER IX

General discussion and conclusions

The object of the present work was the study of the renal excretion of a labelled substance, and if possible to use this substance as a test of the kidney function in various conditions. The new technique of using a radioactive isotope provides us with a much greater opportunity than hitherto for the study of physiologic processes without simultaneous interference with the processes. As the phosphate radical is of such a great biological importance and as this isotope provides properties of great advantage, its ease of preparation, its convenient half life period, the intensity of its radiation, good adaptation for analysis, it seems natural to chose this isotope for an investigation of this type.

An important question to be answered before starting an investigation with radioactive substances in human beings is of course if there are any risks associated with the use of isotopes. With regard to the recent attentions drawn to this problem and referred to in Chapter II, I have used doses of 2 microcuries per kg of body weight, which dosage should meet all the requisities for a safe tracer concentration.

The relation between the specific activity in the urine and in the plasma in certain individuals has been statistically studied in chapter V, (p. 32). It was studied by comparing the ratio S_u/S_b, where S_u and S_b were determinated at an identical time period. To facilitate a comparison between different individuals, I have, from a statistical point of view found it preferable to use the logarithm of this ratio. Thus, when log S_u/S_b is positive the specific activity is greater in the urine than in the blood, and when log S_u/S_b is negative, the situation is reversed.

In the earlier chapters, V and VI, the results obtained for the various groups have been presented separately. In Chapter V the excretion of

P^{32} in normals is discussed. After an intravenous injection, P^{32} can very soon, after about 5 minutes, be found in the urine. After an intramuscular or intraperitoneal injection of P^{32} it also appears in the urine very soon. The excretion of P^{32} increases in the course of the first hour to considerable amounts as compared to the activity of the bloodplasma and after about 20 minutes the specific activity is higher in the urine than in the blood. This is in complete agreement with the results of other investigations, which have beens mainly carried out in animals.

After having summarized the results of the statistical calculations (pp. 35—39) we find that after 20 minutes the log S_u/S_b is positive in more than 75 % of all cases and in all time intervals in the period 30—175 minutes. In this time period therefore the specific activity in the urine is higher than in the blood. The maximum of the difference between the S_u and S_b seems to occur 30 to 60 minutes after the injection.

The fact that the specific activity of the urine is higher than that of blood is known and has been discussed by other authors, principally by GOVAERTS. Summarizing the hypothesis founded on his and others previous observations, I am adding some remarks founded on the present investigation.

Immediately after the intravenous injection, the newly introduced phosphate ions consist exclusively of diffusible, dissociated orthophosphate ions. They are rapidly excreted with the urine and almost at once an equilibrium between the plasma orthophosphate and the urinary orthophosphate is achieved. If no regard need be paid to the possibility of some urine being retained in the uropoietic system, the orthophosphate of the urine is exactly the same as that of the plasma.

It seems, probable however, that also another system of equilibrium exists between the plasma phosphates.

In the left of the two systems illustrated in Fig. 15 ($P_u \rightleftarrows P_b$) the ion exchange is very rapid, in the right ($P_b \rightleftarrows P_x$) it is considerably slower. P_x is not orthophosphate, though behaving in some respects like it, and its presence results in a dilution of the specific activity of the plasma.

First when the ion exchange between P_b and P_x has reached an equilibrium a dilution of the specific activity at the analysis no more takes place.

This argumentation is based on a supposed exchange equilibrium between the excreted phosphate and the phosphate compounds of the kidney itself (see discussion and Fig. pp. 57—59).

In individuals with renal disease, the pattern of the excretion of P^{32}, digresses from that of normal children. In group G the values for S_u were lower than those for S_b. However, simultaneously with the disappearance of the clinical symptoms of the renal disease, the values of the S_u rise to a normal level and exceed those for S_b.

This decrease in the S_u cannot be the result of a change of the specific activity during the passage through the glomerulis. The glomerular filtrate must therefore be mixed with other additional amounts of unlabelled phosphate during the passage through the tubular system. Furthermore this unlabelled phosphate must come from the kidney itself. The phosphate excreted through the renal tubules is in an exchange equilibrium with phosphate compounds of the kidney. In renal damage phosphorus compounds, including the orthophosphate of the kidney, are for some reason or other not in an exchange equilibrium with the orthophosphate of the plasma as in the healthy kidney. The decreased or altered metabolism of the diseased kidney may result in a disturbance in the phosphate metabolism so that the turnover of P^{32} to the kidney is itself decreased. The mechanism of this metabolic disturbance is of course not clear. An acidosis in tissues may conceivably constitute the origin. On the other hand an acidosis may be symptomatic of a reduced metabolism.

The problem of the renal function in prematures and in newborn children is of a great physiologic and pediatric interest. From the important investigations of McCance, Dean, West, Rubin, Smith, Chasis, Barnett, Vesterdal, Tudvad and others, we know that in premature and also full term, newborn babies, there is a reduced renal function. West, Smith and Chasis found that clearance values, corresponding to those of adults, are obtained somewhere between the 2nd—3rd and the 8th—10th month. This lower glomerular filtration rate in early infancy may have an anatomical explanation in the finding of Gruenwald and Popper, that there is a persistance of a foetal type of epithelial membrane, a thick layer of cells, surrounding the capillary tuft in the glomeruli. They concluded that this would be likely to impede filtration. Other histological examinations of the kidneys of young human foetus reveal, that the juxtamedullary glomeruli are more completely formed than the cortical glomeruli, which in the earlier stages of development do not even seem to resemble glomeruli (Trueta). Such a difference in size

and character of these two groups of glomeruli is not observed in the normal adult kidney. In the foetal and neonatal life the cortex makes up a much smaller proportion of the total renal substance than it does in adult life, with a corresponding predominance of the medulla. Thus the foetal kidney is structurally immature and some of the premature infants are required to put into function those immature kidneys. POTTER sets the division between the mature and immature kidney at about 35 weeks'gestation.

These histological facts may explain the decreased phosphate clearance, but we must not forget the influence of the endocrine glands. With regard to the phosphate excretion we know, for instance, that the parathyoid hormone increases the excretion of phosphorus. We know too that posterior pituitary hormone causes a blanching of the glomeruli and a cessation of the glomerular blood flow with a consequent reduction in glomerular filtration. The rate of reabsorption of water in the distal tubules is influenced considerably by a hormone secreted by the posterior pituitary. HELLER suggests that in early infancy the posterior, pituitary-renal mechanism is not fully developed and the tubules function imperfectly.

In this study, the group of prematures had a very low $Cl_p = 1.2 \pm 0.29$, ml/min.

The histological characteristics and the hormonal regulations of the premature kidney, however, can not explain the decreased S_u.

As in the diseased kidney the explanation for this finding must be in some alteration of the general metabolic activities of the premature kidney. Some factor must operate which results in a delay in the achievment of an equilibrium between the P^{32} and the phosphates in the renal parenchyma.

The diabetic offers some patterns of interest. In one of the cases (case 89) there was a decreased excretion of P^{32} when the patient was in a state of acidosis. That girl had no clinical signs of nephropathy and at a later examination when she was free from symptoms of acidosis, showed a completely normal excretion curve. As for the other diabetics, who had an abnormal excretion of P^{32} three of the cases had clinical signs of nephropathy. The other two cases had had their disease a long enough time to be expected to have complications. One of them (case 86) had an inulin clearance of 79 and a phosphate clearance of 8, which in this group was rather low, but otherwise no clinical symptoms.

The other girl (case 88) with a duration of her diabetes of 10 years had quite normal clearance values and no clinical signs of renal disturbances. In these cases it is possible, that the reduced P^{32} excretion is an initial and important sign of an early renal damage.

As for the Cl_p it seems remarkable that the values are rather high for the whole diabetic group, also for the cases with a manifest nephropathy. For the uncomplicated cases $Cl_p = 24.03 \pm 2.35$, for the complicated cases $Cl_p = 18.3 \pm 4.31$.

A study of the Cl_{IN} and Cl_{PAH}, which are consequently determined in the diabetic group, shows that the values range within wide limits. In 6 cases the Cl_{IN} is less than 100. Two of those cases had a manifest nephropathy (cases 84 and 85), one of them had only a decreased P^{32} excretion. The other three cases had no signs at all of renal damage. I am quite conscious of the fact that the accuracy of those values might be questionable. The values of Cl_{PAH} seem to range within still more wide limits and it is not possible to conclude the significance of them. In no case, however, did the Cl_{PAH} shows a remarkable value.

It has been impossible to demonstrate clear cut correlations between either the Cl_p and the inulin- and PAH clearances, or between the P^{32} excretion and the normal clearance tests.

As early as 1933, WHITE and MONAGHAN pointed out that the phosphate clearances are not directly related to the plasmaphosphate level, that they were absolutely irregular and therefor of no use as renal function tests. As appearant from table 24, my own figures for the different groups are very different.

TABLE 24

Cl_P in the different groups

	n	$\bar{x}$	s
N_2	23	9.8 ± 1.60	7.8
N_1	15	1.2 ± 0.29	1.1
G	27	2.8 ± 0.41	2.1
N_2K	12	6.7 ± 1.0	3.5
S	19	24.1 ± 2.35	12.8
S_1	7	18.3 ± 4.31	11.3

n = number of determinations
$\bar{x}$ = mean values
s = standard deviation
S_1 = diabetics with renal complication

In the groups G and N_1, however, we find low values through out and in those groups one might be able to demonstrate a correlation between Cl_p and the P^{32} excretion. This, however, is not possible in the group of diabetics with nephropathy.

One can sum up the results of this investigation with the following points:

1. After the injection—intravenously, intramuscularly, or intraperitoneally—of radioactive phosphorus in infants and children with a normal renal function, the specific activity found in urine is within a short time, after 20—40 minutes, higher than in that of the blood.

2. In individuals with an injured kidney for example with a glomerular nephritis, the excretion of P^{32} is decreased and the values of the specific activity with few exceptions fall below these of the blood. From this one may suggest that the determination of the P^{32} excretion of the ratio between the specific activity in urine and in blood at a certain point of time would be a useful test of kidney function.

3. The determination of the P^{32} excretion in diabetic children reveals that a disturbance of this excretion occurs not only in cases with clinical symptoms of renal insufficience, but also in cases where the duration of the diabetes is great enough that a nephropathy might be probable, but where no clinical signs of it have appeared. Possibly further comparisons with clearance tests will show that the determination of the renal excretion of P^{32} is a most sensitive one.

4. The renal excretion of P^{32} in prematures is considerably decreased and is correlated with the clearance of phosphate.

Summary

The purpose of the present investigation was to study the renal excretion of a labelled phosphorus compound in normal and pathological conditions and to examine the possibility of using the values of the exchange between plasma orthophosphate and urine orthophosphate as a renal function test. A comparison between this test and other commonly used renal tests was made in one group.

The first chapter is a very short survey, or rather a résumé, of the literature of the development of the renal physiology. A special section in this chapter is given to the renal phosphate excretion.

In the next chapter the use of radioactive isotopes in general and the use of radioactive phosphorus in particular are discussed. The safeguards for the use of isotopes in humans is emphasized.

The renal excretion of P^{32} was studied in a total of 101 individuals, 96 infants and children and 5 adults. Of these, 28 were normals, among them the 5 adults; 15 were prematures and 63 represented various diseases affecting the kidneys.

The 28 normal individuals were used as a control group.

The investigations were performed on hospitalized children. The technical procedure is described in Chapter III. The determinations of orthophosphate in blood and urine were carried out according to a routine method used at the Wenner-Gren Institute, specifically the Fiske-Subbarow method with Brigg's modification as described by Lindberg (1946). The determination of radioactivity was also performed according to the routine methods of this institute.

After an intravenous injection, P^{32} can very soon, after about 5 minutes, be found in the urine. The excretion of P^{32} increases, in the course of the first hour to considerable amounts as compared to the activity of the blood and, after about 20—40 minutes the specific activity is higher in the urine than in the blood. This is in complete agreement

with the results of the other investigations, which, however, were carried out mainly in animals. The fact that the specific activity of urine is higher than that of blood has been discussed.

In individuals with diseased kidneys, nearly all of the cases being acute glomerulonephritis, the excretion of P^{32} is altered from the pattern found in children with normal renal function. The specific activity of the urine is lower than that of the bloodplasma. The decreased specific activity of the urine in disease is apparantly due to a disturbance of renal metabolism.

In prematures the specific activity in the urine is much lower than that of bloodplasma. They, as in the children with a glomerulonephritis, also show very low phosphate clearances.

In a special chapter is given an account of diabetic children, all treated with insulin and a free diet. In those cases the inulin- and the PAH clearances were also determined. No significant correlation between the clearance values and the P^{32} excretion could be stated. A decreased specific activity of the urine was found in a case in acidosis, who at another occasion showed a normal P^{32} excretion. In two cases of diabetes in which the duration of the disease was 8—10 years, there was a low specific activity in the urine though these children did not show any clinical signs at all of nephropathy. It is suggested that the determination of the relation between the specific activity in the urine and in the blood might be a more sensitive test of early renal disturbance than those now commonly employed.

Case reports

Below, brief reports will be found of all cases in the Groups N_1, G, F, N_2K and C. In Group S, only 6 cases with symptoms of nephropathy have been included, one with but occasional symptoms. The other cases in that group are uncomplicated from the point of view of the renal function and therefore they have been excluded.

Also, all cases of Group N_2 have been excluded. Important data concerning the cases in the Groups S and N_2 will appear from the Tables 21 and 7, respectively.

Case 29, J. W., 43/49, boy, born 1949. He was a twin, admitted with his brother as a premature. The delivery was not remarkable. Birth weight 1.300. At first there were cyanotic attacks and edema. He maintained a position of opisthotonos during his half-a-year in the hospital. He was anemic from the first, falling rapidly to 6.6 gm % Hg and 2.1 mill RBC. Repeated blood transfusions were necessary. Bone morrow examination revealed reduced erythropoesis. After transfusions and irontherapy, the blood picture improved, showing during his last months at hospital, relatively normal values, Hb 11.8 gm % and 4.73 mill RBC. During the first month, the general condition was extremely bad, on two occasions he appeared moribund but recovered. Because of the opisthotonus he had repeated lumbal punctures, revealing increasing amounts of cells, WBC. as high as 89/kbcm. Spinal fluid cultures were negative. The spinal fluid pleocytosis was interpreted as an aftereffect of an intracranial hemorrhage. The prognosis seemed to be bad. His weight on discharge was 4.870.

Diagnoses: Congenital debility and intracranial hemorrhage.

Case 30, F. K., 89/49, girl, born 1949. She was born 11 weeks prematurely, normal parturition and birth weight 1.620 gm. After admission on day of birth she required oxygen for a week and hot water bottles for 5 weeks. Her progress was normal.

Diagnosis: Prematurity, uncomplicated.

Case 31, K.P., 319/49, boy, born 1949. Born 12 weeks before term, weight 2.200 gm. The delivery was not remarkable. He was given a formula and was admitted on May 9th 1949. When discharged he was weighing 3.460 gm on July 13th 1949.

Diagnosis: Prematurity, uncomplicated.

Case 32, B. F., 333/49, boy, born 1949. He was a twin, born in occiput anterior with no signs of asphyxia, birth weight 2.070 gm. The mother, a sero-positive treated luetic, had an attack of pyelitis during pregnancy. He was admitted on May 16th 1949, at primarily days, because of failure to gain weight. At first he was given breast milk. He gained weight regularly to 3.500 gm at discharge. His general condition was good the whole time. Standard serologic tests for syphilis were all negative. Skeletal x-rays showed no luetic changes. Discharged in good general condition.

Diagnosis: Twin premature, uncomplicated.

Case 33, B. O., 371/49, boy, born 1949. He was delivered without difficulty 8 weeks before term. The pregnancy was uncomplicated. Birth weight was 2.000 gm. He was admitted on June 7th 1949, when 5 days old. His general condition was and remained good. His growth was good and he weighed 2.600 gm at discharge July 26th 1949.

Diagnosis: Prematurity, uncomplicated.

Case 34, E. B., 310/49, girl, born 1949. Born 12—13 weeks prematurely, birth weight 880 gm. The parturition was normal and the cause of the prematurity unknown. She lost weight to 740 gm and then increased to 3.700 gm, at discharge, at 3 months. She required incubator case for 7 weeks and at 2 weeks had severe attacks of cyanosis. Though in bad condition, she recovered and then progressed normally.

Diagnosis: Prematurity, uncomplicated.

Case 35, N. W. 370/49, boy, born 1949. He was 7 weeks premature. Birth weight 1.910 gm. Delivery was not remarkable. He had mild cyanotic attacks. He was transferred to Norrtull's Hospital on the day of birth, June 4th 1949. He was kept in an incubator for a few weeks. During the first few days he had a lowered prothrombin index. He thrived and at his discharge weighed 2.990 gm. The mother had sufficient breast milk and he was able to suckle during the last weeks before discharge, July 29th 1949.

Diagnosis: Prematurity, uncomplicated.

Case 36, U. J., 333/49, girl, born 1949. She was born 6—8 weeks prematurely, birth weight 1.500 gm. The delivery was not remarkable and she developed normally.

Diagnosis: Prematurity, uncomplicated.

Case 37, N. T., 404/49, boy, born 1949. He was born 6 weeks before term, birth weight 2.300 gm. The mother had earlier borne a premature child (12 weeks before term) that died after 24 hours. No cause for the prematurity could be ascertained. He was admitted June 30th 1949, on his 6th day of life. During the first two weeks of life there was fairly severe icterus. At first he was tube-fed. Hot water bottles were required to maintain his temperature satisfactorily. There was a mild umbilical infection which faded away after 10 days. He grew well, increasing from 2.080 gm on admission to 3.040 gm at discharge. The mother had throughout a fair supply of breast milk. Suckling was initiated

during the last days at the hospital and proceeded well. He was discharged on Aug. 15th 1949 in good condition.

Diagnosis: Prematurity, uncomplicated.

Case 38, L. L., 478/49, boy, born 1949. He was born on Aug. 12th 1949, 13 weeks before term, birth weight 1.020 Gm. The delivery was not remarkable. The lowest weight was 860 gm. There were repeated cyanotic attacks during the first week and on some occasions respiratory standstill lasted as long as 10 minutes. On and off during that time there was a continuous cardiac murmur, due, probably, to a persisting ductus arteriosus. He developed normally. During the first month he was apathetic and could suck a nipple only after some time, but during the last few weeks, took feedings by nipple well. On discharge Nov. 7th 1949 he weighed 2.900 gm.

Diagnosis: Prematurity, marked, uncomplicated.

Case 39, B. N., 475/49, girl, born 1949. She was born 4 weeks before term, birth weight 1.990 gm. The parturition was normal and the reason for prematurity was unknown. Her progress was normal.

Diagnosis: Prematurity, uncomplicated.

Case 40, O.L., 510/49, boy, born 1949. He was born Aug. 21st 1949, 6 weeks before term. The delivery was not remarkable. Birth weight 1.950 gm. He was transferred to Norrtull's Hospital from the maternity hospital on Sept. 29th having followed a normal course. The lowest weight was 1.740 gm and he weighed 1850 on admission. His progress was uninterrupted and he was discharged Oct. 1949, weighing 2.750 gm.

Diagnosis: Prematurity, uncomplicated.

Case 41, E. N., 486/50, girl, born 1949. She was delivered two weeks before term, birth weight 2.400 gm. Discharged at age of 10 days, weighing 2.390 gm. She was apathetic and took feedings poorly with resultant growth failure and consequently was admitted to the hospital. There she did well and was discharged on Dec. 12th, weighing 3.000 gm and in good general condition.

Diagnosis: Prematurity, uncomplicated.

Case 42, H. L., 552/49, girl, born 1949. Delivered 8 weeks before term by cesarean section when the mother developed eclampsia; birth weight 1.490. After 3 weeks she was able to graduate from the incucator. With pyelitis, at 3 weeks, there was a temporary albuminuria which disappeared quickly after treatment.

Diagnosis: Prematurity. Acute pyelitis.

Case 43, E. B., 19/50, girl, born 1949. She was delivered 5 weeks before term, birth weight 1.880 gm. The delivery was normal and the reason for prematurity unknown. Following admission on the day of birth she progressed normally.

Diagnosis: Prematurity, uncomplicated.

Case 44, E. L., 697/46, girl, born 1940. She was from an allergic family and had previously had eczema. Two weeks before admission she had a cold and developed urticaria. After several days she had facial swelling and, later, new urticarial lesions. Hematuria appeared the day prior to admission. During the

first week of hospitalization she had a fever, macroscopic hematuria and albuminuria, hypertension, azotemia, a highanti streptolysin titre and an increased ESR. There was no oliguria. Subsequently, there was a gradual improvement in all of the abnormal findings. Urinary finding during the last month at the hospital were practically stationary with albuminuria 0.3—0.5 ‰, 3—20 RBC per field in the urine sediment. A concentration test was not abnormal and she was not anemic. During hospitalization, her general condition was good throughout.

Diagnosis: Acute glomerulonephritis.

Case 45, H. S., 46/47, boy, born 1941. This boy had repeated upper respiratory infections, recurring otitis with spontaneous perforation, and paracentesis, as recently as in 1945. Early in 1946, he had acute angina tonsillitis and, possibly, pneumonia with hilar adenitis. He was admitted to Norrtull's Hospital for observation of his persistent infection. His tonsils were hypertrophic ragged and congested. Five days after admission there was a flare up of the infection with fever, tachycardia 21.000 WBC., increase in the ESR from 37 to 54 mm, and an enlargement of the cervical glands. Sulfathiazole was administered and following day the urine, previously quite normal contained large numbers of RBC. The sulfathiazole was discontinued. The temperature fell, but the ESR increased to 64 mm and the antistreptolysin titre, doubled to 700 units. Also, small quantities of albumin appeared in the urine. An acute nephritis seemed to be developing but the urinary findings decreased. During his last week at the hospital there was no albuminuria, though there was 5—10 RBC per field in the sediment.

Diagnosis: Acute glomerulonephritis.

Case 46, M. N., 111/47, girl, born 1936. On Jan. 23rd 1947 she developed a common cold. On Feb. 2nd she had acute otitis with temperature up to 40 C. After paracentesis, the fever disappeared but she had increasing weariness, listlessness and apathy and developed edema in the face. The urine was not checked until after a week when albuminuria and hematuria were found. On Feb. 15th she was transferred from the other hospital. At this time she had signs of a serious nephritis, facial edema, hematuria, albuminuria 6 gm per 1000 ml. The NPN was 213 mg%. On the following day there was severe pain in the right ear and signs of mastoiditis. As there was no improvement, she was transferred to another clinic on Feb. 17th for surgical treatment. Following treatment the nephritis cleared completely.

Diagnosis: Acute glomerulonephritis.

Case 47, G. H., 282/47, girl, born 1942. She was admitted on April 28th 1947 from another hospital where she had been treated for an otitis, and where a nephritis developed. There was a hematuria, 20 RBC per field but there was no albumin. She improved rapidly and the ESR which was 45 at admission, rapidly decreased. The hematuria decreased but persisted minimally. When discharged, May 31st 1947, her general condition was good. Continued confinement to bed at home was persisted.

Diagnosis: Acute glomerulonephritis.

Case 48, L. K., 439/47, boy, born 1938. Early in May 1947 he developed a slight angina with a fever, which disappeared after a few days. On May 18th

facial edema was noted and, on the following day, the urine was dark. A doctor was consulted and he discovered an acute nephritis. The fever and edema vanished after a few days. At admission June 9th 1947, there was albumin and many RBC in the urine. The albuminuria subsided within a week but the RBC persisted. After Sept. 9th, he was allowed 4 to 5 hours daily in the open air. He gained weight and was afebrile. ESR was 6, and the urine was normal except for 5 to 6 RBC per field. He was discharged on Oct. 25th, convalescing satisfactorily.

Diagnosis: Acute glomerulonephritis.

Case 49, R. A., 692/47, boy, born 1944. He has been followed since July 1945 for a hepatosplenomegalia. In Oct. 1947 he developed albuminuria and hematuria with a NPN of 52 mg%; blood pressure normal. After 3—4 weeks had the albumin disappeared but the hematuria remained for about 2 months. The serum protein were normal. A biopsy of the liver showed a cirrhosis of the Laënnec type. Subsequent studies showed a normal liver biopsy, normal liver function tests and a complete disappearance of all abnormal renal findings.

Diagnosis: Acute glomerulonephritis in a case of cirrhotic liver, (postinfectious or Banti's disease?)

Case 50, L. J., 716/46, boy, born 1938. This boy previously treated at Norrtull's Hospital for nocturnal enuresis (environmental damage), was admitted for acute nephritis. Somatically, he was well until 2 months before admission, when he had an acute tonsillitis with fever for one week. Following this he was tired and ill and developed swelling around the eyes. His doctor found albuminuria and microscopic hematuria. On admission he had facial edema, a blood pressure of 160/110, NPN 46—49 mg%, ESR 15—20 mm., antistreptolysin titre 500, but no hemolytic streptococci from pharyngial cultures. After a fortnight he was afebrile and the admission finding had improved. The RBC in the urine decreased to about 20 per field, and the albuminuria contained until a tonsillectomy two months later.

Diagnosis: Acute glomerulonephritis.

Case 51, K.-E. B., 110/48, boy, born 1941. Two weeks before admission he developed an infection of upper respiratory tract and had a fever for a few days, followed by faintness. The development of facial edema and macroscopic hematuria. When admitted, on Feb. 10th 1948 he was not very ill but had a somewhat swollen face, no fever, a sedimentation rate of 39, an antistreptolysin titre of 800, a moderate rise in blood pressure. The NPN was 64 mg%. There was still macroscopic hematuria and a + + albuminuria. There were hemolytic streptococci in the nose and pharynx. The NPN sedimentation rate, hypertension and abnormal urinary findings diminished rapidly. After 1 1/2 month, all findings were normal, except for the presence of 4—0 red corpuscles per field of vision in the urinary sediment, which persisted. He was discharged on May 21st 1948.

Diagnosis: Acute glomerulonephritis.

Case 52, M. S., 45/49, girl, born 1939. At Christmas time in 1948, she had a cold, that disappeared after 10 days. About Jan. 10th, she suddenly developed

a swelling in the face. The school doctor found an albuminuria. She ran a low grade fever and had a cough during the week before admission. When admitted on Jan. 19th she had a slight albuminuria and isolated RBC in the urinary sediment. The edema and albuminuria disappeared in a few days but the urine sediment continued to show an occasional RBC. Though a diagnosis of nephrosis was entertained at the time of admission the error of this entertainment was soon evident. She was discharged in very good general condition on March 9th.

Diagnosis: Acute glomerulonephritis.

Case 53, L. W., 136/49, boy, born 1939. He fell ill in Feb. 11th with fever, a headache and angina. On Feb. 15th sulfonamide treatment was started and by the 18th he became almost afebrile, afterwards running a low grade fever. He began to complain of abdominal pain and vomited slightly. On Feb. 19th, these troubles increased and the urine was found to be bloody. When admitted on Feb. 20th he had macroscopic hematuria, albuminuria, oliguria and a high NPN. A hypertonic glucose solution was given intravenously and diuresis ensuldü. The urine was normal thereafter. A concentration test showed a possibly somewhat deficient concentration. He was discharged home on March 3rd 1939, in good condition.

Diagnosis: Acute glomerulonephritis.

(The diagnosis of sulfonamid poisoning was discussed but the history suggests, in all probability, an acute glomerulonephritis.

Case 54, K. S., 634/49, boy, born 1944. From the age of 8 months he always had dark urine with fever. In Nov. 1948 he was treated at Sachsska Children's Hospital for a nephritis which followed measles. On discharge from there he had only occasional RBC in the urinary sediment. He grew worse at home and was transferred to Norrtull's Hospital, where the examination, including pyelography and cystoscopy, revailed no abnormalities. Following discharge he was followed in the out patient clinic where 10—15 RBC were occasionally found in the urinary sediment. He was lively and troublesome, when confined to bed and as his mother worked evenings he was readmitted on Oct. 17th. The hematuria was more marked. He was afebrile. The hemature subsided promptly and he was discharged to a convalescent home on Oct. 29th. Later, he was again followed in the out patients clinic.

Diagnosis: Subacute glomerulonephritis? Unidentified renal malfomation?

Case 55, E. L., 212/49, girl, born 1937. She previously had a persistently high ESR that could not be explained. On March 30th she began to vomit and on March 31st had fever. Her doctor found a pharyngeal infection and albumin, RBC and casts in the urine. The fever persisted for three days and the patient was admitted to the hospital. On admission, April 4th, she had pneumonia and otitis media. The urine was floody, but after 10 days the urine was free of albumin and the sediment normal. She was afebrile after the first day. The NPN was normal throughout. Discharged free from symptoms on May 4th.

Diagnosis: Acute glomerulonephritis.

Case 56, C.-H. G., 280/49, boy, born 1947. He was admitted because of a persistent albuminuria, discovered 7 months before when he consulted a doctor for listlessness after following a throat infection about a month before. His urine also had a number of RBC and casts in the sediment. The ESR was 46. This reaction was thought to be an acute glomerulonephritis. He was not admitted at once. On admission after three weeks there was albuminuria but the sediment was normal. He was discharged but because of the persistent albuminuria, admitted again for observation after about a month. The findings were unchanged and he was again discharged in good general condition.

Diagnosis: Subacute glomerulonephritis. Further controls have improved a suspect chronical nephropathy.

Case 57, L. S., 435/49, boy, born 1943. On July 3rd he began to vomit and on July 7th to have hematuria. In the week prior to admission he had some irregular fever. On July 17th he developed facial edema. Albuminuria and hematuria were found by the doctor he consulted. On July 18th at admission he was not very ill but had gross hematuria. He improved rapidly and was free of symptoms and had clear urine after 2 weeks. He was discharged as well on August 22nd.

Diagnosis: Acute glomerulonephritis.

Case 58, L. S., 389/49, girl, born 1945. She fell ill on July 9th 1949, with fever and a sore throat. On July 16th the urine was dark-coloured. At admission July 19th there was facial edema. Discharged on Aug. 22nd albuminuria, hematuria and pyuria. She improved rapidly and discharged Aug. 22nd fever free, with clear urine and an ESR of 15. Subsequently she was normal.

Diagnosis: Acute glomerulonephritis.

Case 59, U. P., 765/49, girl, born 1940. She fell ill, during a scarlatina epidemic in her school, with angina, fever and swollen cervical glands, without an exanthem or desquamation. When admitted on Nov. 18th 1949, with a temperature of 40.4 C, she was not ill. Hemolytic streptococci were cultured from the pharynx. The urine contained large numbers of RBC and albumin. She was given penicillin and was afebrile within 4 days. After 2 weeks the urine was entirely clear and she had a normal ability to concentrate. The NPN, which was 80 mg%, fell. When discharged on Dec. 22nd urinary findings were normal, though the ESR was 25 mm. She was readmitted on Dec. 29th 1949 with a temperature of 39 C. At admission the urine contained 10 to 15 RBC in the sediment. NPN was 50 mg%. She was afebrile after a day's penicillin treatment and after 2 days the urine was normal, likewise NPN and a concentration test. Discharged home on Jan. 12th 1950 in improved condition, still confined to bed because of the ESR, 26 mm.

Diagnosis: Acute glomerulonephritis (Focal nephritis?).

Case 60, A. H., 687/49, girl, born 1939. She became ill, during a scarlatina epidemic, with angina and a fever but without an exanthem or desquamation. There were hemolytic streptococci in pharynx and she was treated with a sulfonamide. After 3 weeks she again became febrile with edema of the eyelids and hematuria. When admitted on Dec. 2nd 1949, there was edema of the face,

a rise in blood pressure, albuminuria and hematuria, increased ESR, 46 mm. There was a rapid improvement, she became afebrile, the blood pressure fell and the urine cleared. At discharge on Dec. 22nd 1949, the ESR was 15 mm, NPN 24 mg%, the urine clear, except for RBC in the sediment. A concentration test was normal.

Diagnosis: Acute glomerulonephritis.

Case 61, E. H., 752/49, girl, born 1939. She had angina early in Dec. 1948 and fell ill, with a fever, on Christmas Eve. She voided small quantities of dark coloured urine. At admission she did not seem sick. There was albuminuria and minimal microscopic hematuria. The blood pressure was 125/80. The heart was slightly dilated. After a few days the urine was entirely clear. There was no rise in blood pressure. The ESR was down to 29 mm at discharge. The antistreptolysin titre remained high, 3.200 units. She was discharged to be followed in the out patient's department.

Diagnosis: Acute glomerulonephritis.

Case 62, K. S., 109/50, girl, born 1942. This 8 year old girl had previously been hospitalized for bronchopneumonia and sinusitis at the age of 4, in Nov. 1948. She was found to have albuminuria and a minimal hematuria which was interpreted as a nephritis; nursed at home. This cleared and she was normal until in May 1949 when an albuminuria was again found after an otitis. In Oct. her urine was again normal. When admitted, Feb. 7th 1950, she again had albuminuria and WBC 15 field of vision. After admission the urine showed no albumin, on many examinations, occasionally there was isolated WBC. The blood pressure and blood values were normal. The NPN was 40 mg%. Her concentration ability was normal. There was no evidence of infection but the ESR was 25. She was afebrile all the time. Staying up failed to provoke albuminuria. The diagnosis of orthostatic albuminuria was considered but seemed unlikely.

Diagnosis: Acute glomerulonephritis.

Case 63, C. S., 342/50, girl, born 1941. On March 3rd 1950 she developed a sore throat and, 8 days later, an ESR of 25 and albuminuria. On March 23rd she had edema of the face with 3 gms of albumin per 1.000 ml and occasional RBC in the urine. When admitted, April 14th, she was in good general condition, but during hospitalization she always had albumin in urine, 0.9—3.0 gms per 1.000 ml., though practically no RBC in the sediment. The ESR ranged from 55 down to 25 at discharge. The NPN was normal. The throat culture showed no hemolytic streptococci but the antistreptolysin titre was elevated. She was discharged on June 21st 1950 in good condition, but later observations showed evidence of chronic nephritis.

Diagnosis: Acute glomerulonephritis (Later chronical).

Case 64, A. Å., 168/47, girl, born 1937. At the end of Dec. 1946 she became ill with a fever and sore throat, which lasted less than a week. On Jan. 7th she had edema of the eyelids. When examined, Jan. 10th, at the outpatients' department she was found to have dark cloudy urine with many red cells and

albumin. She complained of being tired. Admitted on Feb. 12th 1947. After 4 weeks, ESR was 28 mm, urinary sediment improved, and a tonsillectomy was perfo:med. After that, she got gradually better. The nephritis persisted and after 4 months' treatment she was transferable to a convalescent home for continued rest. At this time the NPN and a concentration test were normal. ESR was 15, the urine was free of albumin and showed 2—3 red cells in the sediment.

Diagnosis: Acute glomerulonephritis.

Case 65, H. J., 238/47, boy, born 1933. From Oct. 1946 he had not been well and ate poorly. Urine was not examined. In Feb. 1947, when he was admitted to a hospital for maxillary sinusitis, an examination of the urine showed albumin and sparse amount of red corpuscles. When he was admitted to this hospital, March 17th 1947, albumin and large numbers of RBC were present in the urine. After a month, the urine was free from albumin and contained only occasional RBC. He was discharged, home, on May 21st 1947, for continued rest.

Diagnosis: Acute glomerulonephritis.

Case 66, L.-I. B., 162/47, boy, born 1937. At the end of Dec. 1946, be became ill with a fever and general pains, all disappearing within 3—4 days. On Jan. 9th 1947, he developed facial swelling and had dark-coloured urine, positive for albumin. When admitted on Jan. 13th 1947, there was edema of the face, reddened tonsillar crypts, a softly systolic heart murmur at the base. Blood pressure 150/100, urine albumin .1—.2 ‰ with 20—30 RBC per field, ESR 36 mm, AST 1.000, NPN 46 mg% and slight hypochronic anemia. By x-ray examination the heart was enlarged but the EKG was normal. No hemolytic streptococci was found in the throat cultures. When discharged on May 17th 1947, general condition very good. The urine was albumin free and showed only 3—5 RBC. per field.

Diagnosis: Acute glomerulonephritis.

Case 67, M. A., 283/47, girl, born 1934. For weariness and facial swelling a doctor was consulted. When admitted April 29th 1947, there was moderate edema, macroscopic blood in the urine, albuminuria increased blood pressure, oliguria and azotemia. She was first placed on a sugar diet, then on milk and wegetables and finally on a low protein regime. Antistreptolysin titre was constantly high. Penicillin was administered. The findings were uncharged and within a week the prognosis seemed bad. At the beginning of June she deteriorated with a rise in non-protein nitrogen and a further decrease in urination. The serum albumin values were constantly increased. A blood transfusion brought no improvement. For a week a diuretic was given, with moderate effect; discontinued owing to patient's refusal to take it. The general condition grew continuously worse. She died of uremia on June 14th 1947. Autopsy was refused by parents.

Diagnosis: Acute glomerulonephritis. (One might question this diagnosis. Several factors suggest a chronic rather than acute nephritis.)

Case 68, A. E., 523/49, girl, born 1945. In mid Sept. 1949 she had a sore throat and had a low grade fever for some days, afterwards felt tired and out of sorts.

On Sept. 21st 1949, an inceptive swelling of her face was noted and the urine was dark. The day before albumin had been found in the urine of the father, who fell ill with angina soon before the onset of the patient's illness. Her urine was tested. When admission, Sept. 22nd, the urine contained albumin and many RBC. Hemolytic streptococci were cultured from the pharynx and the AST eas 4:000. The NPN was 29 mg‰. She was given penicillin for 10 days. The sedimentation rate began to fall. The urine was normal after 10 days.

She was discharged, home, on Nov. 4th, in good general condition, to remain in bed.

Diagnosis: Acute glomerulonephritis.

Case 69, B. W., 135/50, girl, born 1940. She had scarlatina in Autumn 1949, a mild case. She was found to have albuminuria by chance. Just prior to admission the urine became darker. She was admitted on Febr. 1st 1950, to the Samariten Children's Hospital, where she showed slight redness in pharynx and gross hematuria and + albuminuria but no edema. A month later the urine was somewhat clearer but still showed + albuminuria and 10–15 RBC per field in the sediment. Later observations have shown that she has a chronical nephritis.

Diagnosis: Acute glomerulonephritis (Later chronical).

Case 70, K. B., 1476/50, boy, born 1945. About 20th February 1950 he developed a sore throat with fever up to 39 C, lasting for a week. On March 3rd 1950 he again had fever of 39 C and soreness of the neck muscles and the following day his urine was grossly bloody. When admitted on March 5th 1950 he had edema of the face, hematuria and albuminuria. The course of his illness was protracted for about 6 months, then he recovered.

Diagnosis: Acute glomerulonephritis.

Case 71, K. P., 94/47, boy, born 1938. This boy had an acute onset on Jan. 13th 1947 of bronchial catarrh with a temperature of 39.4 C. A doctor was not consulted. The patient soon developed chills, and a temperature of 41.2 C. At the same time, his urine was very dark, almost black. He had slight nausea and a headache, and seemed swollen around the eyes. On admission Jan. 28th 1947, he was febrile, and the urine was grossly bloody. After penicillin, he was afebrile. The urine cleared rapidly, but even on his discharge, Feb. 24th, RBC were present in the sediment, the Addis count showing 3.01 mill. He was restricted to bedrest at home.

Diagnosis: Acute glomerulonephritis.

Case 72, G. S., 64/47, girl, born 1942. She was treated at Norrtull's hospital in 1944 for acute nephritis and endocarditis. She was discharged free from albumin and with normal sediment. Her urine, on a single examination in 1945, was free from albumin. She was admitted, on Dec. 9th 1946, with an acute hemorrhagic nephritis that set in one week after a throat infection. During this period, the albumin, as well as the RBC in the urine, disappeared very rapidly. She was afebrile. There were no abnormal cardiac findings, except for a slight backward bulge, disclosed by x-ray. Examination of the blood revealed

nothing abnormal. ESR was 30 mm. Her NPN was a little high at first, then became normal. She went home over Christmas, and was readmitted on Jan. 7th for continued treatment. The nephritis was completely cured. A tonsillectomy was performed on Jan. 20th 1947. Her general condition was good when discharged on Feb. 10th.

Diagnosis: Acute glomerulonephritis (recurrence).

Case 73, Å. B., 65/47, boy, born 1942. Without any previous symptoms, infection or disease, he, on Jan. 13th 1947, showed a swelling around the eyes and a bloated face. He was irritable though playing as usual. On Jan. 15th his urine was a brownish red colour. On Jan. 17th he had a temperature of 39.3 C and was vomiting. On the following day his temperature was normal but on Jan. 20th, again a fever. On admission, Jan. 20th, he was slightly edematous but otherwise the physical examination showed no abnormalities. The urine remained macroscopically bloody, until the week before discharge, when examination of the sediment disclosed a rapid and conspicuous improvement, with only occasional RBC and no albumin. Except for a mild acute sinusitis his general condition was satisfactory, with a good appetite during the whole time. He was discharged on Feb. 22nd for continued treatment at home. The course was prolonged but, in May 1947, he was free from symptoms and was not followed further.

Diagnosis: Acute glomerulonephritis.

Case 74, K. K., 121/47, boy, born 1939. At the middle of Jan. 1947 he had bronchial catarrh with a temperature of 39 C. He was afebrile after some days, but felt tired and was troubled by a cough and nasal catarrh. He improved after 3 weeks but, on Feb. 5th, again felt ill. In the afternoon of Feb. 6th he had a chill with a temperature of 39 C, which increased to 40 C the following night. During that day, the urine turned darkbrown. During this period a slight facial swelling developed. There was vomiting but no headache. After admission, on Feb. 7th, the albuminuria cleared, and the marked hematuria improved, though an Addis count showed 12.84 million RBC. At discharge, on March 4th, there was a persistant sinusitis and a secondary anemia, Hb 65 %. There were no local changes which indicated a need for a tonsillectomy. He was to remain in bed at home.

Diagnosis: Acute glomerulonephritis.

Case 75, J. M., 213/47, boy, born 1936. During the past few years he has had frequent elevations of temperature in connection with upper respiratory infections. In Jan. 1947 he had a slight cold with two temperature peaks of 39 C. In March he had cloudy urine, facial swelling and albumin in his urine. When admitted, on March 11th, he ran a low grade fever. His tonsils were somewhat enlarged and cleft. No other foci of infection were found. There was edema of the ankles without evidence of carditis. The blood pressure was 165/90. There was no anemia and the blood proteins was normal. There was albuminuria .5 gm per 1.000 ml, and a marked hematuria. At discharge, on May 17th 1947, he was in good general condition. There was no albuminuria but there

were 0—5 RBC per field, a case of acute nephritis with continued pathologic sediment. He was to remain in bed at home.

Diagnosis: Acute glomerulonephritis.

Case 76, L. Å., 145/47, girl, born 1943. At the end of January she had a parotitis (probable a lymphadenitis) with a fever of 38 C for 2 days. The swelling subsided within 2 days. She was out of bed for 6 days, seemingly completely recovered. On Feb. 9th her mother noticed that the urine was dark brown. Her doctor diagnosed acute nephritis and prescribed a diet and bed rest. On Feb. 13th, her temperature was 38.7 C and she had pains in her left ear. The urine was not as dark and she had no edema. For 2 days she had a dough. When admitted on Feb. 14th 1947 she had a common cold and was feverish, with red cheeks. She had slight swelling around the eyes, but otherwise no edema. She had albuminuria and the sediment was fairly profuse with RBC. Her urine was soon albumin free, but the sediment persistently contained RBC. On June 3rd there was no albuminuria, but the RBC in the urine sediment varied from 6 to 30 per field. Discharged on June 14th.

Diagnosis: Acute glomerulonephritis, acute sinusitis and acute otitis media.

Case 77, M. A., 355/47, girl, born 1942. About May 15th 1947, she became ill with sore throat, vomiting and a temperature of 39.9 C. Her doctor prescribed a sulfonamide. She became fever free for a day or so and then ran a low grade fever for 3—4 weeks. A week after the recurrence of the fever blood was discovered in the urine. When admitted to Norrtull's Hospital, June 4th 1947, the urine was free of albumin but contained numerous RBC in the sediment. These gradually decreased to an occasional RBC in the next two weeks. The urinary amounts were small. The antistreptolysin titre of 3.600 fell to 1.400 units/ml. Penicillin was given during the first fortnight at this hospital, and, subsequently, for another week in connection with the removal of nasal polypi on July 21st. When discharged on Aug. 20th 1947 she was free from symptoms.

Diagnosis: Acute glomerulonephritis (sulfonamide intoxication?).

Case 78, I. S., 452/47, boy, born 1938. At the beginning of March 1947, he fell ill with a high fever and a headache. His doctor found an albuminuria. After a week his temperature fell, but after another week, symptoms, suggestive of measles appeared. He was then confined to bed for about 7 weeks on a moderate diet. Then for 5 weeks he was out of bed and given a free diet. He appeared quite healthy, but showed a constant albuminuria. On admission, June 13th 1947, there were no physical abnormalities, except a faint systolic murmur at the apex. No hemolytic streptococci were found. The urine was constantly negative, no albumin and nothing pathologic in the sediment. Examination of the blood revealed nothing abnormal. Discharged home on June 17th, as well.

Diagnosis: Status post nephritidem. Post nephritis, type undetermined.

Case 79, D. W., 508/48, boy, born 1947. In May 1948 he became ill, appeared pale, lost his appetite and began to cough, but was afebrile. When admitted to another hospital, an anemia was found. Hgb 64 per cent and RBC 3.5 mill. Albumin was found in the urine but the sediment was normal. Because he

showed difficulty in swallowing solid food, the esophagus was x-rayed, disclosing a rather slow passage in the lower part. He was re-admitted in July 1948. The blood values had improved but there was variably an albuminuria, as much as 0.6 %. Occasional RBC were present in the sediment. He was transferred to Norrtull's Hospital on July 30th. A variable albuminuria was constantly present, though the sediment was always normal. An Addis' count showed 1.2 mill. RBC. The blood pressure was 140 with subsequent falling values. A concentration and dilution test showed specific gravities persistently between 1.010—1.011. Intravenous urography failed twice even with 50 % of umbradil, indicating a marked reduction in the renal secretory capacity. Retrograde pyelography revealed normal pictures bilaterally. Following discharge he seemed more alert and to be better at home, gaining weight. NPN was normal. Urinalysis, however, persisted in showing moderate numbers of RBC and albumin. Hypertension and slight anemia were also constant.

Diagnosis: Chronic glomerulonephritis.

Case 80, B. K., 684/49, boy, born 1945. He developed on Oct. 23rd 1949, pains in abdomen, then 4 days later, scrotal swelling and generalized edema. There was oligmia but no other symptoms. On admission, Nov. 2nd, there was a + + albuminuria with granular casts in the sediment. He was transferred from another hospital, with a diagnosis of acute nephritis, with edema. The edema increased slowly and the albumin in the urine also increased to a maximum of 24 gm per liter. Electroforesis showed a typical nephropatic diagram. There was extreme hypoalbuminemia increased α-globulin and β-globulin and a low γ-globulin. The serum cholesterol was as high as 1.123 mg%. After a period of fever in early March there was a sudden change for the better. The urinary output increased, the edema disappeared, and the lost 18 kg. in weight when discharged, June 2nd. The albumin was 0.5 gm per liter and he was in a very good condition. Subsequently the albumin disappeared and there had been no relapse.

Diagnosis: Nephrotis.

Case 81, K. E., 50/50, boy, born 1945. Early in Jan. 1950, he developed swelling of the legs, particularly over the tibiae, an increasing facial edema, which waxed and waned. For a week he tired easily and then developed a fever to 38.5 C, which remained for two or three days. He was put to bed and gradually became more apathetic. A few days prior to admission he developed pain in the right ear. On Jan. 15th he began to vomit and to have diarrhea. He was able to retain liquid food. No hematuria was observed. When admitted to Norrtull's Hospital, Jan. 20th he was a small boy with multiple malformations (polydactylism, cheiloschisis etc.). The NPN and blood pressure were normal. Serumprotein 3.7 %. Cholesterol 411 mg%. Albuminuria of 4 gm per 1.000 ml without hematuria was present. There was a slight general edema. Penicillin was administered. He was discharged home on Feb. 22nd after considerable improvement.

Diagnosis: Nephrosis. Malformation.

Case 82, L. H., 76/49, boy, born 1943. A boy, aged 5 years, became ill a few weeks before admission on June 11th 1948 with generalized edema. During the whole period of observation he had severe albuminuria as much as 24 gm per

1.000 ml. The serum protein were very low and showed extreme changes of the nephrotic type. The NPN was generally normal or only slightly elevated. The urine sediment was normal or showed rare RBC. There was no hypertension. The BMR was normal. ECG normal. His condition has varied greatly with marked fluctuation in the edema, maximum weight 26.1 kg, minimum 20 kg. The serum cholesterol was as high as 937 mg%. Treatment with a high protein diet, low salt had no particular effect. For a time the administration of serum albumin yielded a distinct improvement. He was discharged unchanged on Dec. 14th 1948. From time the dietary regiem. At discharge, he was temporarily in unusually good condition, with the lowest recorded weight.

Diagnosis: Nephrosis.

Case 83, A. C., 30/50, boy, born 1948. The patient developed normally during the first year of life. Increased normally in weight and at 1 year of age weighed 10.6 kg. He was administered AD-vitamin treatment in June 1949. At examination in Oct. 1949 in spite of the profylactical treatment, the patient manifested distinct signs of richets with enlargement of the epithyses, as well as leftsided radius fracture acquired at a fall a few days earlier. Admitted in a hospital and treated until Jan. 12th with Ea and AD-vitamins. In the Autumn, had failed to increase in weight, with bad apetite. He had no infection. On Oct. 31st, blood calcium 10.8 mg%, phosphorus 4.7 mg%. Phosphate 68 units. Admitted to Norrtull's Hospital on Jan. 13th 1950. Treated with great amounts of D-vitamin. After one month's treatment considerable improvement. Phosphate and calcium values in serum getting normal, the phosphatase decreased from 94 to 39.9 units. No signs of coeliac disease. No symptoms of cystinuria, normal pyelogram. BMR normal. Increased mobility, gets up and stands with support. Plays well with toys. Has begun to say a few words. Calm and sunny temper. However, no definite change in the enlarged epiphyses. No craniotabes. Closed fontanel. Discharged in good general condition.

Diagnosis: Richets, resistent to D-vitamin.

Case 84, B.-D. S., 469/49, boy, born 1939. He had been hospitalized several times for diabetes which developed during his 2nd year. Early it was difficult to regulate his insulin dosage and he was admitted several times in coma or pre coma. His lever was markedly enlarged but function tests were normal. During the year before admission he showed albuminuria but no hypertension or azotemia. The serum albumin was slightly decreased. The eyegrounds had shown hemorrhages during the last 6 months.

Diagnosis: Diabetes mellitus, Retinopathy, Nephropathy.

Case 85, I.-M. P., 629/49, girl, born 1936. She had been hospitalized earlier several times for her diabetes mellitus. She was readmitted on Nov. 8th 1949 in a precoma, which was dealt with in the usual manner. The insulin requirement was high, the blood sugar irregularly elevated. She was difficult to regulate and showed a ketosis readily. Otherwise her condition was good. A high ESR was unexplainable. Her urine occasionally contained albumin. The concentration test was normal but the creatinine clearance was inadequate, (72). The albumin

globulin ratio of 0.4 and an abnormal Takata test indicated parenchymal damage of the liver and kidneys. The ESR was 36 mm, Hn 86 % and NPN 22 mg%. Eye-grounds normal.

Diagnosis: Diabates mellitus. Nephropathy. Hepatopathy.

Case 86, S. T., 267/50, girl, born 1938. Though she had been admitted twice in precoma, for the control of her diabetes, which dated from 1943, she was usually well regulated and in good condition.
There had occasionally been a slight albuminuria, no retinopathy, azotemia or hypertension.

Diagnosis: Diabetes mellitus. Nephropathia?

Case 87, G. I., 304/50, girl, born 1936. She had been hospitalized several times for her diabetes, which was discovered when she was 9 months of age. She had been seen frequently and had readily controlled on a free diet with insulin. Her liver was always enlarged and in 1949 a needle diopsy showed marked fatty infiltration, takata test normal. Thymol test 2 unites. There had never been albuminuria, pathological urinary sediment, hypertension or elevation of the NPN. The eye-grounds showed a rethinopathy with small hemorrhages.

Diagnosis: Diabetes mellitus. Diabetic retinopathy.

Case 88, M. S., 347/50, girl, born 1938. Her diabetes dated from 1940. She was usually very well balanced with regard to insulin and controlled ambulatory. There had never been any evidence of retinopathy or nephropathy.

Diagnosis: Diabetes mellitus.

Case 89, B. B., 685/50, girl, born 1935. This girl, who developed diabetes in 1947, had been hospitalized 7 times to regulate her insulin dosage. Her insulin requirements were very great. She has never shown signs of nephropathy or retinopathy and her NPN and blood pressure have always been normal.

Diagnosis: Diabetes mellitus.

Bibliography

Addis, T.: Glomerular Nephritis. Diagnosis and Treatment. New York, 1948.

Albright, F., Bauer, W., Ropes, M. and *Aub, J. C.:* J. Clin. Inv. 7: 139—181, 1929.

Albright, F. and *Ellsworth, R.:* J. Clin. Inv. 7: 183, 1929.

Albright, F., Burnett, C. H., Parson, W., Reifenstein, E. C. Jr, and *Ross, A.:* Medicine, 25, 399, 1946.

Ambard, L.: Physiologie Normale et Pathologique des Reins. Paris, 1931.

v. Bahr, G.: Acta Med. Scand. Suppl. CLXXXVI, 1947.

Barnett, H. L.: Proc. Soc. Exper. Biol. and Med. 44, 634, 1940.

— Pediatrics. 5, 2, 1950.

Bernard, C.: Lecons sur le Diabète et la Glycogenèse Animale. Paris, 1877.

Bessière, E.: Arch. d'Ophtalmologie. 49, 219, 1932.

Best, Ch. H. and *Taylor, N. B.:* The Physiological Basis of Medical Practice. Baltimore, 1950.

Bowman, W.: Phil. Tr. Roy. Soc., London, 57—80, 1842.

Brandt, J. L. and *Gruhn, J. G.:* Am. J. Physiol. 153, 458, 1948.

Briggs, A. P.: J. Biol. Chem. 53, 13, 1922.

Brull, L.: Compt. rend. Soc. de Biol. 122, 76, 1936.

Cambier, P.: Ann. de méd. 35, 273, 1934.

Cantarow, A. and *Trumper, M.:* Clinical Biochemistry. Philadelphia and London 1946.

Chaikoff, J. L.: Physiol. Rev. 22, 291, 1942.

Chasis, H. and *Smith, H. W.:* J. Clin. Invest. 17, 347, 1938.

Croom, H. J. and *Scott, G. I.:* Lancet. 1. 1949.

Cushny, A. R.: The Secretion of the Urine. London, 1926.

Dahlberg, G. and *Grill, C.:* Acta Med. Scand. suppl. CLXX, 1946.

Dahlberg, G., Jorpes, E., Kallner, S., Lichtenstein, A.: Acta Med. Scand. suppl. CLXXXVIII, 1947.

Darrow, D. C., da Silva M. M. and Stevensen, S. S.: f. Pediatr. 27, 43, 1945.

Debré, R.: Le syndrome de Diabète renal. Paris, 1931.
Dean, R. F. A. and *McCance, R. A.:* J. Physiol. 106/4, 431, 1947.
— J. Physiol. 107/2, 182, 1948.
Dolger, B. J.: Am. Med. Ass. 134, 1289, 1947.
Duke-Elder, W. S.: Brit. J. Ophth. 1927, Suppl.
Earle, D.: Bull. New York Acad. Med. 48, 50 1950.
Ekehorn, G.: Über die Intergrative Natur der Normalen Harnbildung. Helsingfors, 1938.
— Acta med. Scandinav. 122, 396, 1945.
— Acta Med. Scandinav. 126, 3, Suppl. CLXXXV, 1946.
Elsom, K. A., Bott, P. A. and *Shiels, E. H.:* Am. Physiol. 115, 548, 1936.
Engel, A.: Nord. Med. 43, 902, 1950.
Erf, L. A., Tuttle, L. W. and *Lawrence, J. H.:* Ann. Intern. Med. 15, 487, 1941.
Fanconi, G.: Jahrb. f. Kinder heilk.. 133, 267, 1931.
— 147, 299, 1936.
— Helv. paed. Acta. 1, 183, 1946.
Fiske, C. H. and *Subbarow, Y.:* J. Biol. Chem. 66, 375, 1925.
— 81, 629, 1929.
Friedländer, H. D. and *Wilde, W. S.:* Am. J. Physiol. 168, 1951.
Gérard, P.: J. Anat. 70, 354, 1936.
Gottlieb, R. and *Magnus, R.:* Arch. f. exper. Path. u. Pharmacol. 45: 223, 1900.
Govaerts, J.: Bull. Ac. Roy. Méd. Belg. V—VIII, II, 624, 1943.
— Bull. Soc. Chimie Biol. 29, 1—3, 1947.
— Nature. 160, 53, 1947.
— Arch. Int. de Pharmacodynamie et de Thérapie. 75/3—4, 261, 1948.
Grill, C.: Nord. Med. 37, 487, 1948.
Gruenwald, P. and *Popper, H.:* J. Urol. 43, 452, 1940.
Guest, G. M. and *Rapoport, S.:* Physiol. Rev. 21, 410, 1941.
Hahn, L. and *Hevesy, G.:* Acta Physiol. Scand. 3, 193, 1942.
Hahn, T. F. and *Hevesy, G.:* Kgl. Dansk Videnskapl. Selskab. Biol. Medd. 15, 5, 1940.
Hanum, S.: Diss. København, 1938.
Harrison, H. E. and *Harrison, H. C.:* J. Clin. Inv. 20, 47, 1941.
Heidenhain, R.: Pflüger's Arch. J. d. ges. Physiol. 9, 1, 1874.
Heller, H.: J. Physiol. 102, 429, 1944.

Hevesy, G. and *Chiewitz, O.:* Nature 1, 136, 1935.
Hevesy, G.: Radioactive Indicators. New York, 1948.
Hilden, T.: Diss. København, 1946.
Hoffman, W. S., Parmelee, A. H. and *Grossman, A.:* Am. J. Dis. Child. 75, 637, 1948.
Hogeman, O.: Clearance tests in renal disorders and hypertension. Diss. Upsala, 1948.
— Acta Med. Scand. Suppl. CCXVI, 1948.
Hood, B.: Studies on renal function. Diss. Stockholm, 1950.
John, H. J.: The Journal of Pediatrics. 35, 6, 1949.
Josephson, B.: Nord. Med. 25, 222, 1945.
Joslin, Root, White, Marble and *Beiley:* Treatment of diabetes mellitus Phil. 1946.
Kamen, M. D.: Radioactive Tracers in Biology. New York, 1947.
Kimmelstiel, P. and *Wilson, C. I.:* Am. J. Path. 12, 83, 1936.
Kinsey, V. E. and *Grant, W. M.:* J. Gen. Physiol. 26, 119, 1942.
Kjellberg, S. K. and *Rudhe, U.:* Acta Radiologica. 31, 3, 1949.
Kjerulf-Jensen, K.: Acta Physiol. Scand. 3, 1, 1941.
Klinke, K.: Der Mineralstoffwechsel. Leipzig—Wien 1931, Quoted from Gaedertz, 1936.
Krogh, A.: Proc. Roy. Soc. s. B. 133, 140, 1946.
Laake, H.: Nord. Med. 31, 1668, 1946.
— Acta Med. Scand. Suppl. CLXVIII, 1945.
Lambert, P. P., Van Kessel, E. and *Leplat, C.:* Acta Med. Scand. 128/4, 386, 1947.
Lambrechts, A.: C. R. Soc. Biol. 122, 468, 1936.
Lawrence, J. H.: J. Am. Med. Ass. 134, 3, 1947.
Lewine, S. Z. and *Gordon, H. H.:* Am. J. Dis. Children. 274, 64, 1942.
Lichtenstein, A.: Acta pediatrica. 42, 1753, 1949.
— Bull. Schweiz. Akad. de Med. Wissenschr. 48, 3, 97, 1947.
Lind J. and *Karlberg P.:* Acta Pæd. 39, 454, 1950.
Lindberg, O.: Arkiv för Kemi, Mineralogi och geologi. Diss. Bd. 23 A, no. 2, 1946.
Lippman, R. W.: Am. J. Physiol. 154: 532, 1948.
— Am. J. Physiol. 155: 282, 1948.

Low-Beer, B. V. A.: The clinical use of Radioactive Isotopes. Springfield, Ill. 1950.

Ludwig, C.: Nieren und Harnbereitung. Wagner's Handwörterbuch der Physiologie. Braunschweig, 1844.

Lundsgaard, E.: Skand. Arch. f. Physiol. 72, 267, 1935.

McCance, R. A.: Lancet 1, 823, 1936.

— Schw. Med. Wchschr. 76, 857, 1946.

— Physiol. Rev. 28, 331, 1948.

— Acta Paediatrica, 36, 1948.

McCance, and *Young, W. F.:* Arch. Dis. Childhood.

McCrory, W. W., Forman, C. W., McNamara, H. and *Barnett, H. L.:* Am. J. Dis. Children 80, 3, 1950.

Marinelli, L. D., Quimby, E. H. and *Hine, J. G.:* Am. f. Roentgenol. and Rad. Ther. 59, 260, 1948.

Marshall, E. K. and *Vickers, J. L.:* Bull. Johns Hopkins Hosp. 34, 1-7, 1923.

Muller, J. H.: Schweiz. Med. Wchschr. 77, 236, 1947.

Möllerström, J.: Das Diabetesproblem. Leipzig 1943.

— Nord. Med. 36, 257, 1947.

O'Donoghue, O.: Trans. Ophtal, Soc. U. K. 51, 637, 1931.

Palm, E.: On the Phosphate exchange between the blood and the eye. Diss. Lund, 1948.

Pitts, R. F.: Am. J. Physiol. 140, 535, 1943.

— Am. Rev. Physiol. 8, 199, 1946.

Potter, V. R.: J. Biol. Chem. 169, 17, 1947.

Quimby, E. H.: Am. J. Roentgenol. and Rad. Ther. 58, 741, 1947.

Raaschou, H.: Chronic Pyelonephritis, Copenhagen 1948.

— Nord. Med. 44, 1593, 1950.

Rehberg, P. B.: Biochem. J. 20, 447, 1926.

— Biochem. J. 20, 461, 1926.

Richards, A. N.: Urine formation in the amphibian kidney, Harvey Lect., 93, 1934—1935.

Robinson, H. W. and *Nelson, W. E.:* Am. f. Dis. Children 69, 323, 1945.

Rosenbusch, H.: Ann. Paediatrici 164, 1945.

Shannon, J. A.: Am. f. Physiol. 112, 405, 1935.

— Physiol. Rev. 19, 63, 1939.

Shannon, J. A., Farber, S. and *Troast, L.:* Am. J. Physiol. 133, 752, 1941.

Shannon, J. A. and *Fisher, S.:* Am. J. Physiol. 122, 765, 1938.

Smith, C. A.: The Physiology of the Newborn Infant. Springfield, Thomas, 1946.

Smith, H. W.: Lectures on the Kidney, Lawrence, Kansas, 1943.

— Bull. of the New York Acad. of Med. 23/4, 1947.

Ström, L.: Acta Paed. Suppl. 77, 160, 1949.

Swedin, B.: Personal Communication.

de Toni, G.: Acta Paed. 16, 479, 1933.

Tron, E.: Arch. f. Ophth. Graefe 119, 659, 1928.

Trueta, J., Barcley, A. E., Daniel, P., Franklin, K. J. and *Prichard, N.M.L.:* Studies of the Renal Circulation, Oxford, 1947.

Vesterdal, J.: Acta Paed. 37, 5—6, 1949.

Vesterdahl, J. and *Tudvad, F.:* Acta paed. 37, 5—6, 1949.

Volhard, F.: Die doppelseitigen Hämatogenen Nierenkrankheiten, Berlin, 1918.

Walker, A. M.: J. Biol. Chem. 101, 269, 1933.

Walker, A. M. and *Hudson, C. L.:* Am. f. Physiol. 118, 130, 1937.

Wallgren, A.: To be published in Arch. Kinderheilk.

Wearn, J. T. and *Richards, A. N.:* Am. f. Physiol. 71, 209, 1924.

West, J. R., Smith, H. W. and *Chasis, H.:* J. Pediatr. 32, 10, 1948.

White, H. L. and *Monaghan, B.:* Am. J. Physiol. 104, 412, 1933.

White, Priscilla and *Waskow, E.:* South Med. J. 41, 561, 1948.

Winternitz, R. and *Stary, Z.:* Ztschr. f. d. ges. exper. Med. 89, 540, 1933. Quoted from Krause 1934.

Wolf, A. V.: The Urinary Function of the Kidney, New York, 1950.

— Am. Journ. of Physiology 148, 1, 1947.

Young, W. F., Hallum, J. L. and *McCance, R. A.:* Arch. Dis. Childhood, 16, 243—252, 1941.

Östling, G.: Intern. Physiolog. Congr. Copenhagen, 1950.

Zusammenfassung

Der Zweck dieser Untersuchung ist das Studium der renalen Aussonderung einer radioaktiven Phosphor-Verbindung unter normalen und unter pathologischen Bedingungen, ferner die Prüfung der Möglichkeit, die Werte des Austausches zwischen dem radioaktiven Plasma-Orthophosphat und dem radioaktiven Urin-Orthophosphat als eine renale Funktionsprobe zu benützen. Für eine Gruppe wurde ein Vergleich durchgeführt zwischen dieser Probe und anderen, gewöhnlich benützten, renalen Funktionsproben.

Das erste Kapitel ist eine sehr kurze Übersicht der Literatur der Entwicklung der renalen Physiologie. Eine besondere Abteilung dieses Kapitels befasst sich mit der renalen Phosphor-Aussonderung.

Im nächsten Kapitel werden im Allgemeinen die Verwendung der radioaktiven Isotopen und im Besonderen die Benützung des radioaktiven Phosphors besprochen. Die für die Verwendung von Isotopen bei Menschen erforderlichen Vorsichtsmassnahmen werden diskutiert.

Die renale Aussonderung von P^{32} wurde bei zusammen 101 Individuen studiert, und zwar bei 96 Säuglingen und Kindern und bei 5 Erwachsenen. Das Material bestand aus 23 gesunden Personen, darunter die 5 Erwachsenen, aus 15 vorzeitig geborenen Kindern und aus 63 Personen, bei denen verschiedene Affektionen der Nieren vertreten waren.

Die 23 gesunden Individuen wurden als eine Kontrollgruppe verwendet.

Die Untersuchung wurde an Kindern durchgeführt, die sich im Spital befanden. Der technische Vorgang ist im Kapitel III beschrieben. Die Bestimmungen des Orthophosphates im Blut und im Harn wurden auf Grund der routinmässigen Methode durchgeführt, die im Wenner-Gren Institut verwendet wird, insbesondere auf Grund der Methode

von Fiske-Subbarrow mit der Modifikation von Brigg, wie sie von Lindberg (1946) beschrieben wurde. Die Bestimmung der Radioaktivität wurde gleichfalls auf Grund der bei dem genannten Institut üblichen Methode vorgenommen.

Nach einer intravenösen Injektion kann P^{32} sehr schnell, nach ungefähr 5 Minuten, im Harn festgestellt werden. Im Laufe der ersten Stunde wächst die Aussonderung von P^{32} auf einen im Vergleich mit der Aktivität im Blute beträchtlichen Betrag an; nach ungefähr 20 bis 40 Minuten ist die spezifische Aktivität im Harn höher als im Blut. Dies ist in vollständiger Übereinstimmung mit den Ergebnissen anderer Untersuchungen, die sich jedoch hauptsächlich auf Tiere beziehen.

Bei Personen mit einer Nierenaffektion — es handelte sich in fast allen Fällen um eine akute Glomerulonephritis — ist die Ausscheidung von P^{32} verschieden von dem Bilde, das bei Kindern mit normaler Nierenfunktion festgestellt wurde. Die spezifische Aktivität des Harnes ist niedriger als die des Blutplasma. Die erhöhte spezifische Aktivität im Harne im Krankheitszustand ist offenbar auf die Störung des renalen Metabolismus zurückzuführen.

Bei Säuglingen ist die spezifische Aktivität im Harne viel niedriger als die im Blutplasma. Diese zeigen auch, ebenso wie die Kinder mit Glomerulonephritis, sehr niedrige Phosphat-Clearance-Werte.

In einem besonderen Kapitel wird ein Bericht über diabetische Kinder gegeben, die alle mit Insulin und freier Diät behandelt wurden. Für diese Fälle wurden auch die Insulin — und die PAH — Clearance-Werte bestimmt. Es konnte keine signifikative Korrelation zwischen den Clearance-Werten und der Aussonderung von P^{32} festgestellt werden. Eine verminderte spezifische Aktivität im Harne wurde in einem Fall von Acidosis festgestellt, der bei einer anderen Gelegenheit eine normale Aussonderung von P^{32} gezeigt hat. In zwei Diabetes-Fällen, bei denen die Krankheit 8 bis 10 Jahre gedauert hat, ergab sich eine niedrige spezifische Aktivität im Harne, obwohl bei diesen Kindern überhaupt keine klinischen Zeichen einer Nephropathie festgestellt wurden. Es kann angenommen werden, dass die Bestimmung der Relation zwischen der spezifischen Aktivität im Harne und im Blute bei initialen renalen Störungen eine vielleicht mehr empfindliche Probe darstellen kann, als die anderen Proben, die jetzt gewöhnlich benützt werden.

Resumé

L'objet des présentes recherches a été d'étudier l'excrétion rénale de phosphore radioactif, P^{32}, sous des conditions normales et pathologiques et d'examiner la possibilité d'employer les valeurs de l'échange entre le plasma orthophosphate et l'urine orthophosphate comme test des fonctions rénales. Une comparaison entre cette épreuve et d'autres épreuves des fonctions rénales employées généralement a été faite dans un groupe.

Le premier chapitre est un apercu très court, ou plutôt un résumé, de la littérature concernant le développement de la physiologie rénale. Une partie spéciale de ce chapitre traite de l'excrétion rénale de phosphate.

Dans le chapitre suivant on discute l'emploi d'isotopes radioactifs en général et l'emploi de phosphore radioactif en particulier. On discute aussi la manière de protéger les êtres humains lors de l'emploi d'isotopes.

L'excrétion rénale de P^{32} a été étudiée en clinique sur 101 sujets, 96 enfants et 5 adultes. Ce groupe était composé de 23 sujets en bonne santé, dont les 5 adultes, de 15 prématurés et de 63 enfants qui présentaient de différentes maladies affectant les reins.

Les 23 sujets sains ont été employés comme groupe de contrôle.

Les recherches ont été exécutées en clinique sur des enfants. Le procédé technique est décrit dans le 3ème chapitre. La quantité d'orthophosphate dans le sang et dans l'urine a été déterminée selon une méthode de pratique employée à l'Institut Wenner-Gren, notamment la méthode Fiske-Subbarow avec les modifications de Brigg, comme Lindberg l'a décrit en 1946. La présence de radioactivité a aussi été déterminée selon une méthode généralement employée à cet Institut.

Après une injection dans les veines, on peut très vite trouver, après à peu près 5 minutes, du P^{32} dans l'urine. L'excrétion de P^{32} augmente dans le cours de la première heure, en quantité considérable comparée à l'activité décelée dans le sang. Après à peu près 20—40 minutes l'acti-

vité spécifique est plus élevée dans l'urine que dans le sang. Ceci est tout-à-fait conforme aux résultats d'autres épreuves qui, cependant, ont été effectuées principalement sur des animaux. Le fait que l'activité spécifique de l'urine soit plus élevée que celle du sang a été discuté.

Chez les sujets ayant des reins affectés, (presque tous soufraient de glomerulonephritis aigüe,) l'excrétion de P^{32} diverge de l'excrétion trouvée chez les enfants ayant des reins normaux. L'activité spécifique de l'urine est plus basse que celle du plasma du sang. L'activité spécifique réduite de l'urine semble être due à un trouble du métabolisme rénal.

Chez les prématurés l'activité spécifique de l'urine est beaucoup plus basse que celle du plasma du sang. Ces enfants montrent aussi, comme les enfants souffrants de glomerulonephritis, une tres faible élimination de phosphate.

Dans un chapitre spécial on donne un exposé sur les enfants diabétiques, étant tous traités avec de l'insuline et par une diète libre. Dans ces cas on a aussi déterminé l'élimination d'inuline et de PAH. On n'a pu constater aucune relation importante entre les valeurs d'élimination et l'excrétion de P^{32}. Une activité spécifique réduite de l'urine a été trouvée dans un cas d'acidose, qui, une autre fois, montra une excrétion normale de P^{32}. Dans deux cas de diabète, dont la durée était de 8 à 10 ans, il y avait une activité spécifique basse dans l'urine, bien que ces enfants n'aient pas montré du tout de signes cliniques de néphropathie. On suppose qu'en déterminant la relation entre l'activité spécifique de l'urine et celle du sang on arrive à un test plus sensible en ce qui concerne les premiers troubles des reins que par les tests généralement employés maintenant.

Resumen

El objeto de las presentes investigaciones ha sido estudiar la excreción renal de fósforo radioactivo, P^{32}, bajo condiciones normales y patológicas y examinar la posibilidad de emplear los valores del cambio entre el plasma ortofosfato y la orina ortofosfato como test de las funciones renales. En un grupo se ha hecho una comparación entre ésta y otras pruebas de las funciones renales generalmente empleadas.

El primer capítulo es una orientación muy corta, o más bien un resumen, de la literatura relativa al desarrollo de la fisiología renal. Una parte especial de este capítulo trata de la excreción renal de fosfato.

En el capítulo siguiente se discute el empleo de isotopos radioactivos en general y el empleo de fósforo radioactivo en particular. Se trata también la manera de proteger los seres humanos al emplear los isotopos.

La excreción renal de P^{32} ha sido estudiada en un total de 101 individuos, 96 niños y 5 adultos. Este grupo estaba compuesto de 23 sujetos con buena salud, entre ellos los 5 adultos, de 15 prematuros y de 63 niños atacados de diferentes enfermedades en los riñones.

Los 23 individuos sanos han sido empleados como grupo de control.

Las investigaciones han sido ejecutadas en niños hospitalizados. El procedimiento técnico está descrito en el tercer capítulo. La cantidad de ortofosfato en la sangre y en la orina ha sido determinada según un método práctico empleado en el Instituto Wenner-Gren, específicamente el método Fiske-Subbarow con las modificaciones de Brigg, como Lindberg lo ha descrito en 1946. La presencia de radioactividad ha sido determinada también según un método generalmente empleado en este Instituto.

Después de una inyección endovenosa se puede encontrar muy pronto, unos cinco minutos más tarde, P^{32} en la orina. La excreción de P^{32} aumenta en el curso de la primera hora en cantidad considerable com-

parada con la actividad de la sangre. Después de unos 20—40 minutos la actividad específica es más elevada en la orina que en la sangre. Esto está completamente de acuerdo con los resultados de otras pruebas que, sin embargo, han sido efectuadas principalmente en los animales. Se discute el hecho de que la actividad específica de la orina sea más elevada que la de la sangre.

En los individuos con los riñones afectados (casi todos sufriendo glomerulonefritis aguda) la excreción de P^{32} diverge de la excreción encontrada en los niños con los riñones normales. La actividad específica de la orina es más baja que la del plasma de la sangre. La actividad específica reducida de la orina parece ser debida a una turbación del metabolismo renal.

En los prematuros la actividad específica de la orina es mucho más baja que la del plasma de la sangre. Estos niños muestran también, como los niños que padecían glomerulonefritis, una eliminación muy débil de fosfato.

En un capítulo especial se da una exposición sobre los niños diabéticos, todos ellos tratados con insulina y con una dieta libre; en estos casos se ha determinado también la eliminación de inulina y de PAH. No se ha podido comprobar ninguna relación importante entre los valores de eliminación y la excreción de P^{32}. Una actividad específica reducida de la orina ha sido encontrada en un caso de acidosis que, en otra ocasión, mostró una excreción normal de P^{32}. En dos casos de diabetes, en los cuales la duración era de 8 a 10 años, ha habido una actividad específica baja en la orina, aunque los niños no habían mostrado ningunos signos clínicos de nefropatía. Se supone que determinando la relación de la actividad específica de la orina y la de la sangre se llega a un test más sensible en lo que concierne a las primeras perturbaciones de los riñones que por los tests generalmente empleados ahora.

Errata

Page	Line	Change	To
15	15	mm/l	nM/l
16	1	phosphatose	phosphatase
22	12	NH_4PO_4	$(NH_4)_3PO_4$
23	11	A_2	A_b
26	19	N_2HPO_4	Na_2HPO_4
49	11	G_2	G
50	21	145—506	506—145
61	1+5	Insulin	Inulin
86	last	S	S_1
88	14+17	28	23

ICAL LIBRARY

Acta Paediatrica

Vol. 40 · December 1951 · Suppl. 83

UNIVERSITY
OF MICHIGAN

FEB 13 1952

MEDICAL
LIBRARY

THE PROCEEDINGS OF THE TENTH NORTHERN PEDIATRIC CONGRESS STOCKHOLM

JUNE 13—JUNE 16, 1951

EDITED BY

JUSTUS STRÖM
M. D.
SECRETARY GENERAL

Almqvist & Wiksells Boktryckeri AB UPPSALA

List of Supplements to Acta Pædiatrica.

1. **Muhl, Greta,** Über den Stoffwechsel des gesunden, natürlich ernährten Säuglings und dessen Beeinflussung durch Fettreduktion der Nahrung. Sw. Cr. 5: —.
2. **Höjer, J. Axel,** Studies in Scurvy. Sw. Cr. 5: —.
3. **Eriksson, Zaida,** Über Anstaltsschaden der Kinder: »Hospitalismus» in Kinderheimen. Sw. Cr. 3: —.
4. **Drucker, Paul,** Clinical Investigations into the Pathogenesis of Infantile Tetany. Sw. Cr. 3: —.
5. **Wallgren, Arvid,** Contribution à l'étude des splénomégalies de l'enfance. Sw. Cr. 5: —.
6. **Rhodin, Hans,** The Suspension-Stability of the Blood in Scarlatina. Sw. Cr. 3: —.
7. The Proceedings of the Fourth Scandinavian Pædiatric Congress, held at Helsingfors on June 28th—30th, 1927. Sw. Cr. 5: —.
8. **Herlitz, C. W.,** Studien über die Blutzuckerregulierung bei gesunden Säuglingen und solchen mit exsudativer Diathese. Sw. Cr. 3: —.
9. **Widnäs, Karin,** Études sur le diabète sucré chez l'enfant. Sw. Cr. 5: —.
10. **Gyllenswärd, Curt,** Some Sources of Error at Differential Count of White Corpuscles in Blood Stained Smears. Sw. Cr. 3: —.
11. **Salomonsen, Leif,** Periodisches Erbrechen und Ketonämie bei Kindern. Sw. Cr. 5: —.
12. **Wallgren, Arvid,** Erfahrungen über epidemischen Icterus (sog. Icterus catarrhalis). Sw. Cr. 5: —.
13. **Rietz, Einar,** Sterblichkeit und Todesursachen in den Kinderjahren. Sw. Cr. 5: —.
14. **Gyllenswärd, Curt,** Das weisse Blutbild bei Hunger und regelmässiger Nahrungszufuhr. Sw. Cr. 3: —.
15. **Skaar, T.,** Experimental Rickets. Sw. Cr. 5: —.
16. **Toverud, Kirsten Utheim,** and **Toverud, Guttorm,** Studies on the Mineral Metabolism during Pregnancy and Lactation and its Bearing on the Disposition to Rickets and Dental Caries. Sw. Cr. 5: —.
17. **Kloster, Johan,** The Distribution and Frequency of Rickets in one of the Fishery Districts of Finmark and Relation of Diet to the Disorder. Sw. Cr. 5: —.
18. **Svensgaard, Elisabeth,** Blood Sugar in Normal and Sick Children with Special Reference to Coeliac Disease. Sw. Cr. 5: —.
19. **Herlitz, C. W.,** A Contribution to the Knowledge of the Function of the Liver and the Reticulo-Endothelial System, Particularly in Infectious Diseases of Children. Sw. Cr. 3: —.
20. **Henschen, Folke,** Über Christians Syndrom und dessen Beziehungen zur allgemeinen Xanthomatose. Sw. Cr. 3: —.
21. **Bjørn-Hansen, Haakon,** Leukozyten-Untersuchungen bei den Masern. Sw. Cr. 5: —.
22. **Joukovsky, V. P.,** et **Rousskikh, V. N.,** Étude clinique et anatome-pathologique sur la tuberculose des centres nerveux chez l'enfant. Sw. Cr. 3: —.
23. **Huss, Ragnar,** Studien über die Schultz-Charltonsche Auslöschreaktion bei Scharlach. Sw. Cr. 5: —.
24. **Wickström, J.,** Eine elektrokardiographische Untersuchung über das Herz beim Scharlach. Sw. Cr. 3: —.
25. **Schiøtz, Carl,** Eine Darstellung und kritische Bewertung der Ursachen des Rückganges der Säuglingssterblichkeit in Norwegen. Sw. Cr. 5: —.
26. The Proceedings of the Sixth Northern Pediatric Congress, Stockholm August 27—August 29, 1934. Sw. Cr. 5: —.
27. **Rustung, Erling,** Studien über Rachitis. I. Mitteilung. Sw. Cr. 3: —.
28. **Sundal, Alfred,** Chronische infektiöse Erkrankungen der Harnwege im Kindesalter. Sw. Cr. 3: —.
29. **Magnusson, J. Henning,** Zur Kenntnis der Blutveränderungen bei Frühgeborenen. Sw. Cr. 5: —.
30. **Herlitz, C. W.,** Studien über den Krankheitsverlauf und die Therapie des Diabetes mellitus bei Kindern. **Söderling, B.,** Behandlung der Zuckerkrankheit im Kindesalter ohne Diäteinschränkungen. Sw. Cr. 5: —.
31. **Ström, Justus,** Periodisches Erbrechen mit Ketonämie bei Kindern. Sw. Cr. 5: —.
32. **Faxén, Nils,** The Red Blood Picture in Healthy Infants. Sw. Cr. 5: —.
33. **Herlitz, Gillis,** Studien über die Prognose der okkulten Kindertuberkulose. Eine Nachuntersuchung bei tuberkulinpositiven und tuberkulinnegativen Kindern. Sw. Cr. 5: —.

ACTA PÆDIATRICA SUPPLEMENTUM 83

The Proceedings of the Tenth Northern Pediatric Congress

Stockholm
June 13—June 16
1951

Edited by

Justus Ström
M. D.
Secretary General

TRYCKERI A.-B. THULE STOCKHOLM 1951

810650

PRESIDIUM

PRESIDENT: PROFESSOR ARVID WALLGREN
SECRETARY GENERAL: DOCENT JUSTUS STRÖM
EXHIBITION MANAGER: PROFESSOR NILS MALMBERG

THE EXECUTIVE COUNCIL OF THE CONGRESS

Danish Section:

Professor P. PLUM
Professor OLUF ANDERSEN
Dr. P. DRUCKER, secretary
Dr. A. ROTHE-MEYER, substitute

Norwegian Section:

Professor L. SALOMONSEN
Dr. L. STOLTENBERG
Dr. A. NJÅ, secretary
Professor A. SUNDAL, substitute

Finnish Section:

Professor V. RANTASALO
Professor C. E. RÄIHÄ
Professor T. SALMI, secretary
Docent P. HEINIÖ, substitute

Swedish Section:

Professor C. GYLLENSWÄRD
Professor A. WALLGREN
Professor S. SIWE
Docent J. STRÖM, secretary and substitute

MEMBERS OF THE CONGRESS

* Means member of the Northern Pediatric Association.

DENMARK

*Andersen, Aa Ortved, kommunelæge, med fru, Köpenhamn
Andersen, Henning, dr, Köpenhamn
*Andersen, Oluf, professor, med fru, Köpenhamn
Auken, Kirsten, dr, Hellerup
Biering, Axel, dr med., med fru, Köpenhamn
*Bræstrup, P. W., overlæge, Hellerup
Brandt, Sven, dr med., med fru, Hellerup
*Christensen, J. Flamand, overlæge, med fru, Odense
*Drucker, Paul, dr med., Köpenhamn
*Dueholm, Claus, dr, med fru, Köpenhamn
Dupont, Annalise, dr, Hellerup
Egeblad, Knud, dr, med fru, Glamsbjerg
Engbaek-Jensen, Signe, dr, Brønderslev
Fallesen, Mary, dr
Farup, Bodil, Cand. psych., Köpenhamn
*Flensborg, E. Winge, overlæge, med fru, Köpenhamn
Foght-Nielsen, Karen Else, dr, Holte
*Friderichsen, Carl, overlæge, med fru, Köpenhamn
*Friderichsen, Hans, dr, med fru, Köpenhamn
*Friedlænder, Axel, dr, med fru, Köpenhamn
Friis-Hansen, Bent, dr, Köpenhamn
*Gjörup, Ernst, dr med., Gentofte
Gørtz, Grete, dr, Köpenhamn
Hald, Dagmar, dr, Padborg
Hansted, Chr., dr, Köpenhamn
*Heinild, Svend, dr med., Hellerup
*Hertz, Mette, dr, Aarhus
*Holm, Sigrid, dr, Hellerup
Iversen, Torben, dr, Aarhus
Jacoby, Per, dr, med fru, Köpenhamn
*Jersild, Torben, dr, med fru, Köpenhamn
Juel-Nielsen, N., dr, Aarhus
Koch, Jørgen, dr, med fru, Köpenhamn
*Kreutzfeldt, Harald, dr med., med fru, Köpenhamn

KROMANN, AGNETE, dr, Frederiksberg
KROMANN, BOY, dr med., Frederiksberg
LENSTRUP, JØRGEN, dr, med fru, Köpenhamn
LOUS, KAREN, dr, Rungsted Kyst
MUNKVAD, IB, dr, med fru, Köpenhamn
NIELSEN, E. REINHOLDT, dr, Tarm
*PLUM, PREBEN, professor, med fru, Köpenhamn
RICHLEFS, GERTIE, Cand. psych., Gentofte
*SCHIERBECK, N. J., dr, med make, Hellerup
STEVNS, JOHANNE, dr, Herlev
TOLSTRUP, KAI, dr, med fru, Odense
*TRIER KAJ, dr, med fru, Köpenhamn
TUDVAD, FOLKE, dr, Köpenhamn
*ULDALL, CHR., dr., med fru, Hellerup
VESTERDAL, JØRGEN, dr med., Köpenhamn
VESTESEN, ELISABETH, dr, Köpenhamn
*WILKEN-JENSEN, KNUD, dr, med fru, Köpenhamn

FINLAND

*AHLBERG, C. J. L., dr, med fru, Helsingfors
*AHVENAINEN, E. K., docent, Helsingfors
*ARAJÄRVI, TERTTU, dr, Helsingfors
*ARVOLA, ARVO, dr, med fru, Kotka
BASTMAN, LILLY, dr, Stockholm
*DAHLBERG, ULF, dr, Helsingfors
*ERIKSSON-LIHR, ZAIDA, överläkare, Dromsö
ERMALA, P., dr, Helsingfors
*GRÖNLUND, LARS, dr, med fru, Helsingfors
*GRÖNROOS, JARL-AXEL, dr, med fru, Åbo
*HALLMAN, NIILO, docent, Helsingfors
*HALONEN, VILJO, dr, med fru, Helsingfors
*HEINIÖ, PAAVO, överläkare, med två döttrar, Helsingfors
*HELMINEN, SIRKKA-LIISA, dr, med make, Åbo
*HEIKEL, PER-ERIK, dr, med fru, Helsingfors
*HULTIN, HOLGER, dr, med fru, Helsingfors
*JÄNNES, NIILO, dr, med fru, Helsingfors
*JÄRVINEN, TONY INGRID, dr, Helsingfors
*JÄYKKÄ, SIINTO, dr, med fru, Åbo
*KAUHTIO, JYRKI, dr, med fru, Helsingfors
*KENA-WICKSTRAND, LEMPI, dr, med dotter, Helsingfors

*Liakka, Vuokko, dr, Tammerfors
Maasik, Elisabeth, dr, Helsingfors
*Malm, Erik, dr, med fru, Helsingfors
*Munsterhjelm, Anders, dr, Helsingfors
Munsterhjelm, Inga, dr, Helsingfors
*Muroma, U., dr, med fru, Helsingfors
*Otila, Eino, dr, med fru, Tampere
*Paaso, Eino, överläkare, med fru, Kuopio
*Palmberg, Olle, dr, med fru, Åbo
*Pettay, Ossi, dr, Helsingfors
*Rantasalo, Ilari, dr, Helsingfors
*Renkonen, Eva, dr, med make, Åbo
*Roine, K., dr, Helsingfors
*Räihä, C.-E., professor, med fru o. dotter, Helsingfors
*Salmi, Toivo, professor, med fru, Åbo
*Salovius, Inger, dr, Ingå
*Seleste, Ester, dr, Helsingfors
*Simell, Greta, dr, Helsingfors
*Sourander, Bertil, medicinalråd, med fru, Åbo
*Tallqvist, Hans, dr, med fru, Helsingfors
*Tähkä, Hilkka, dr, Helsingfors
*Wass, Yrjö, dr, med fru, Tammerfors
*Wasz-Höckert, Ole, dr, med fru, Helsingfors
*Wegelius, Ruth, dr, Helsingfors
*von Wendt, Dora, dr, Helsingfors
*Wickström, J., docent, med fru, Åbo
*Vuori-Lenko, Hilkka, dr, Helsingfors
Vuoristo, Gunvor, dr, Helsingfors
*Ylppö, Arvo, professor, Helsingfors

ICELAND

Olafsson, Oddur, dr, med fru, Stockholm

NORWAY

Amlie, Richard, dr, med fru, Oslo
*Arnessen, Finn, dr, med fru, Oslo
Bache Wiig, Stig, dr, med fru, Nordstrandhøgda
*Berghoff, Hanna, dr, Oslo
Bjordal, Olav, dr, med fru, Oslo
Dalaker, Sigleif, dr, med fru, Oslo

*Ek, Eyvind, dr, Oslo
*Esp, Erling, dr, med fru, Thondheim
*Hagelsteen, Henrik, dr, med fru, Oslo
Hestetun, Sverre, dr, Oslo
Hvidsten, Thor, dr
*Höynæs, Ivar, dr, med fru, Stavanger
*Imerslund, Olga, dr, Bergen
Kåss, Arne, dr, med fru, Bergen
*Lange-Ahlson, Astrid, dr, med make, Oslo
Letting, O. J. W., dr, Bergen
*Marvel, Odd, dr, Oslo
*Njå, Arne, dr, med fru, Oslo
*Nordahl, Ivar, dr, med fru, Oslo
Olson, Willy, dr, med fru, Oslo
Pedersen, Harald, dr, med fru, Bergen
Reiler, Rolf, dr, med fru, Hvalstad, Asker
*Riis, Dag, dr, med fru, Oslo
*Rinvik, Roald, overlæge, Oslo
*Rosenberg, Per, dr, med fru, Oslo
*Salomonsen, Leif, professor, med fru, Oslo
*Skatvedt, Marit, dr, Oslo
Skjelbred-Knudsen, K. B., dr, med fru, Oslo
*Smith, Anders, dr, med fru, Drammen
*Sundal, Alfred, professor, med fru, Bergen
*Tho, Anders, dr, med fru, Oslo
*Trætteberg, Hedvig, dr, Oslo
*Tönseth, Håkon, dr, med fru, Trondheim
Ugland, Jens, Halvard, dr, med fru, Oslo
Waal, Nic, dr, Aarhus
Wennevold, Leif, dr, med fru, Oslo
Wergeland, Hjalmar, dr, med fru, Oslo
*Vik-Larsen, dr, Stavanger
*Ødegård, Alf, dr, med fru, Oslo

SWEDEN

*Ahnsjö, Sven, docent, med fru, Stockholm
*Alm, Ingvar, dr, Stockholm
Andersson, Åke, dr, Stockholm
*Anzén, Georg, dr, med fru, Saltsjö-Duvnäs
*Appelberg-Ulfsparre, Elsa, dr, Stockholm

Appelbom, Brita, dr, Norrköping
*Axtrup, Sten, lasarettsläkare, med fru, Kristianstad
Barr, Jan, överläkare, Örebro
*Belfrage, Harald, dr, med fru, Göteborg
*Bellman, Margit, dr, Stockholm
Berfenstam, Ragnar, dr, med fru, Uppsala
Berglund, Gunilla, dr, Stockholm
Bergquist, Einar, dr, med fru, Stockholm
*Bjelkhagen, Ingemar, dr, Stockholm
Blume-Westerberg, Gerd, dr, Göteborg
*Brandberg, Olof, lasarettsläkare, med fru, Örebro
*Broman, Birger, docent, med fru, Stockholm
*Böttiger, Erik, livmedikus, med fru, Stockholm
*d'Avignon, Marcel, dr, med fru, Stockholm
*Edgren, Gunnar, lasarettsläkare, med fru, Halmstad
*Ehrenpreis, Theodor, överläkare, Stockholm
*Elgenmark, Olof, lasarettsläkare, med fru, Nyköping
*Elmqvist, Tore, dr, Malmö
*Enell, Herbert, dr, med fru, Stockholm
Englesson, Gunnar, dr, Lund
*Engström, Harry, dr, med fru, Stockholm
Frisell, Erik, lasarettsläkare, Umeå
*Fritsch, Paul, dr, Västerås
*Fränkel, Fredrik, dr, med fru, Eskilstuna
*Frödin, Henry, dr, med fru, Stockholm
Gedda, Erik, överläkare, med fru, Göteborg
*Gezelius, Göran, lasarettsläkare, Östersund
*Gudmundsson, Bengt, dr, med fru, Lidingö
*Gunnarson, Siv, dr, med make, Stockholm
*Gunther, Allan, dr, med fru, Stockholm
*Gyllencreutz, Sara, dr, Stockholm
*Gyllenswärd, Curt, professor, med fru, Stockholm
*Gyllenswärd, Åke, dr, med fru, Uppsala
Hagberg, Bengt, dr, med fru, Uppsala
Haglund, Greta, dr, Stockholm
Hahn, Birger, dr, med fru, Stockholm
*Hamne, Bertil, lasarettsläkare, med fru, Falun
Harding, Gösta, överläkare, Stockholm
Hedqvist, Thomas, dr, Stockholm
*Heineman, Ivar, dr, Stockholm

*Hellström, Sven Gösta, dr, med fru, Solna
*Helmer, Anna, dr, Hälsingborg
*Herlitz, Carl Wilhelm, professor, Stockholm
*Herlitz, Gillis, lasarettsläkare, Linköping
*Hesselman, Bengt Henrik, lasarettsläkare, med fru, Örnsköldsvik
*Hesselvik, Lennart, dr, Uppsala
*Hjärne, Urban, skolöverläkare, Stockholm
Hoffman-Bang, Erik, dr, Stockholm
Holmdahl, Kurt, dr, Göteborg
Holmgren, Börje, dr, med fru, Stockholm
*Hultman, Arne, dr, Stockholm
*Hultman, S. T., dr, Djursholm
*Hybbinette, Robert, dr, Stockholm
*Jacobsohn, Georg, dr, med fru, Stockholm
*Jacobsson, Erik, docent, med fru, Saltsjöbaden
*Jelke, Hugo, lasarettsläkare, med fru, Gävle
*Joachimsson, Sven, lasarettsläkare, med fru, Vänersborg
*Johannsen, Nicolai, dr, med fru, Göteborg
Jonsson, Bengt, dr, Stockholm
*Jorup, Sigvard, dr, med fru, Stockholm
*Josefsson, Einar, dr, Stockholm
Kaar, Edda, dr, Stockholm
*Kaijser, Kurt, lasarettsläkare, med fru, Eskilstuna
*Karlberg, Petter, dr, med fru, Stockholm
Karlén, Karl-Henrik, dr, med fru, Stockholm
Karlström, Fritz, lasarettsläkare, med fru, Karlstad
Keilson, Inda, dr, Stockholm
*Kræpelien, Sven, dr, med fru, Stockholm
*Lagercrantz, Rutger, dr, Stockholm
*Landau, Albin, dr, med fru, Göteborg
*Larsson, Yngve, dr, med fru, Stockholm
Levander-Lindgren, Maj, dr, Stockholm
*Lichtenstein, Henrik, dr, Stockholm
*Lind, John, docent, med fru, Stockholm
Lindahl, Douglas, dr, med fru, Stockholm
Lindahl, Jonas, överläkare, Stockholm
*Lindberg, Gustaf, lasarettsläkare, Norrköping
*Linde, Erik, dr, med fru, Kalmar
Lindquist, Bertil, dr, Lund
*Lindquist, Nils, lasarettsläkare, Hälsingborg

LINGEN, CHRISTIAN, dr, Stockholm
LINGEN, MARIE-LOUISE, dr, Stockholm
*LUNDSTRÖM, ROLF, dr, med fru, Djursholm
*MALMBERG, NILS, professor, med dotter, Stockholm
*MALMGREN, BERTIL, dr, Stockholm
*MANNHEIMER, EDGAR, docent, med fru, Stockholm
*MELIN, KARL-AXEL, dr, Stockholm
*MELLANDER, OLOF, professor med fru, Uppsala
*MOSSBERG, HANS-OLOF, dr, med fru, Stockholm
*MURRAY, UNO, dr, Katrineholm
MÖLLER, TAGE, dr, med fru, Stockholm
*NAGLO, OWE, dr, med fru, son och dotter, Stockholm
NATHORST, HERBERT, dr, med fru, Stockholm
NILSBY, IVAR, dr, Lund
*NORDENFELT, PER, dr, med fru, Stockholm
*NORDLUND, ELSA-BRITA, överläkare, Stockholm
*NORDWALL, ULF, livmedikus, med fru, Stockholm
*NORMARK, ASSAR, lasarettsläkare, med fru, Västerås
NYRÉN-BRENEL, BIRGITTA, dr, Göteborg
*PALMGREN, ÅKE, lasarettsläkare, Visby
PETTERSSON, GUSTAF, överläkare, Göteborg
*PRAG, ANDERS, dr, Karlskrona
*RABO, ERIK, dr, med fru, Karlskoga
*RANKE, SIGURD, dr, Malmö
RANSTRÖM, STIG, dr, med fru, Uppsala
RODHE, GÖSTA, dr, med fru, Stockholm
*RUDBERG, SVEN, dr, med fru, Stockholm
*RYDENSTAM, BO, dr, med fru, Boden
*SELANDER, PER, överläkare, Malmö
SILVERSTOLPE, LENNART, dr, med fru, Stockholm
*SIWE, STURE, professor, med fru, Lund
*SJÖLIN, STIG, dr, med fru, Uppsala
*STERNER, LARS-GÖSTA, dr, med fru, Stockholm
*STRÖM, JUSTUS, överläkare, med fru, Stockholm
STRÖM, LARS, dr, med fru, Stockholm
*SVEDENIUS, GUNNAR, dr, med fru, Stockholm
*VON SYDOW, GERT, lasarettsläkare, Sundsvall
*SYLVAN, HANS, dr, med fru, Stockholm
SÖDERBERG, BERTIL, dr, Lund
SÖDERHJELM, LARS, dr, med fru, Uppsala

*Söderling, Bertil, lasarettsläkare, med fru, Borås
*Thorssell-Lagergren, Karin, dr, Hässleholm
Uddenberg, Gunborg, dr, Lund
*Uddenberg, Inez, dr, Göteborg
*Urwitz, Siegfrid, dr, Stockholm
*Vahlquist, Bo, professor, med fru, Uppsala
*Wahlström, Birger, lasarettsläkare, med fru, Landskrona
*Wallgren, Arvid, professor, med fru och dotter, Stockholm
*Wejdling, Knut, dr, med fru, Stockholm
Vendel, Stephan, dr, Göteborg
*Werner, Birgitta, dr, Stockholm
*Wernstedt, Wilhelm, professor, med fru, Stockholm
Ygberg, Nils H., dr, med fru, Stockholm
Zetterström, Rolf, dr, Stockholm
*Åkerrén, Yngve, överläkare, med fru, Göteborg
*Öberg, Gösta, överläkare, med fru, Uppsala

SWITZERLAND

Zbinden, Christian, dr, Vevey

U.S.A.

Peterson, J. Cyril, dr, med fru, Nashville, Tenn.

FRANCE

Alexandre, Michel, dr, Paris

MINUTES OF THE PROCEEDINGS

Thursday, June 14th, 8.30 a. m.

The president, Prof. A. WALLGREN, opened the Congress

He proposed as vice-presidents:

Prof. P. PLUM, Copenhagen, Prof. C. E. RÄIHÄ, Helsingfors,
Prof. L. SALOMONSEN, Oslo, Prof. S. SIWE, Lund,
Prof. C. GYLLENSWÄRD, Stockholm

Section I

Thursday, June 14th, 9 a. m.—12 a. m.

Prof. A. Wallgren took the chair.

Main Topic of Discussion: Psychosomatic Diseases in Childhood.

Main Speakers:

1 a. Sven Ahnsjö, Sweden: *Psychosomatic Disorders in Pediatric.*

1 b.. Oluf Andersen, Denmark: *Psychosomatic Disease in Childhood.*

1 c. Gunvor Vuoristo, Finland: *Review of a lecture discussing methods of work in psychosomatic pediatrics.*

1 d. Hjalmar Wergeland, Norway: *Asthma as a psychosomatic symptom in children.*

Collaborators:

1 e. Sven Heinild, Denmark: *Present Tasks of Psychosomatic Pediatrics.*

1 f. Siv Gunnarson, Sweden: *Some experience from psychiatric work in a pediatric unit with children suffering from psychosomatic diseases.*

Disc.: P. Plum, C. E. Räihä, B. Vahlquist.

1. Grete Gørtz, Troels Smith, J. Rasmussen, I. Boesen, K. Bierring-Sørensen, P. Drucker, E. Fog, A. Henriques, S. Heinild, H. Kreutzfeld, A. Madsen, G. Ortman, A. Schondal, Denmark: *Overcrowded Flats as Aethiological Moment of Behavior Diseases in Childhood.*

3. K. Wilken-Jensen, Nic Waal, Bodil Farup and Kjeld Bülow, Denmark: *Psychosomatic investigations of asthmatic children.*

Disc.: B. Farup, N. Waal, Z. Eriksson-Lihr, E. Gedda, B. Hamne.

Section II

Thursday, June 14th, 2 p. m.—5 p. m.
Prof. P. Plum took the chair.

4. Karen-Else Foght-Nielsen and Ib Munkvad, Denmark: *Upper respiratory tract infections in childhood from a psychosomatic point of view.*
5. Siinto Jäykkä, Finland: *On the Testmeal Research and Its Psychosomatic Background.*
6. P. W. Bræstrup and G. Ricklefs, Denmark: *The Treatment of Psychosomatic Disorders in Childhood with Special Reference to Treatment Primarily of the Mothers.*
7—8. Torben Iversen, Niels Juel-Nielsen, Flemming Quaade, Kai Tolstrup and Anna Elisabeth Østergaard, Denmark: *On Psychogenic Obesity in Children.*
9. Sven Frandsen og Per Jacoby, Denmark: *Eating Problems in Children.*
   Disc. (papers 7—9): S. Gunnarson and H.-O. Mossberg.
10. Sirkka-Liisa Helminen, Finland: *Einige Gesichtspunkte zum Enuresisproblem bei Volksschulkindern.*
11. G. A. Simell, Finland: *On Factors Influencing the Menarche Age in Finland.*
12. Kirsten Auken, Denmark: *Menarche and Attending Mental Reactions.*
    Disc. (papers 11—12): Z. Eriksson-Lihr, T. Iversen.

Section III

Friday, June 15th, 9 a. m.—12 a. m.
Prof. C.-E. Räihä took the chair.

13. Helga Brandt and Sven Brandt, Denmark: *Electroencephalographic Findings in Patients with Cerebral Palsy* (Little's Disease).
    Disc.: K.-A. Melin, R. Amlie, L. Salomonsen, S. Brandt.
14. Terttu Arajärvi, Finland: *Capillarymicroscopic Examinations of the Conjunctiva Capillaries of Premature Infants and Their Sensitiveness to Adrenaline.*
    Disc.: E. Seleste, T. Arajärvi.

15. Erik Malm, Finland: *Physiological Aspects of the Oxygen Treatment of Premature Infants.*
Disc.: A. Ylppö.
16. E. K. Ahvenainen, Finland: *On Asphyxial Membranes in Lungs of Newborns.*
Disc.: A. Ylppö, S. Ranström, L. Salomonsen, Y. Åkerrén, E. Malm, J. Lind and C. Wegelius, P. Selander.
17. Gustaf Pettersson, Sweden: *Brachyoesophagus and Insufficiency of Cardia in Children.*
18. Jyrki Kauhtio, Finland: *On the Blood Minerals in Pyloric Stenosis Patients.*
Disc.: P. W. Bræstrup, Y. Åkerrén, P. Selander, J. Kauhtio.
19. Viljo Halonen, Finland: *On the Use of Intravenous Fat Emulsions.*
20. P. Ermala, Finland: *Alimentary Chylomicronæmia in Children.*
Disc.: A. Ylppö.
21. Hans Tallqvist, Finland: On the *Pyruvic Acid Content in the Blood of Healthy Children.*
Disc.: O. Andersen, B. Vahlquist, C. E. Räihä, H. Tallqvist.

Section IV

Friday, June 15th, 2 p. m.—5 p.m.
Prof. S. Siwe took the chair.

22. J. Vesterdal and F. Tudvad, Denmark: T_m *for PAH and Glucose in Premature Infants.*
23. J. Vesterdal, B. Friis-Hansen and F. Tudvad, Denmark: *Total and Extracellular Body Water in Children during ACTH Treatment.*
Disc. (papers 22—23): P. W. Bræstrup, F. Tudvad.
24. Arne Kåss, Norway: *Morbus Hæmolyticus Neonatorum in One of Dizygotic Twins.*
25. Olga Imerslund, Norway: *Red Blood Cell Diamters in Megaloblastic Anæmia in Children Needing Continuous Treatment.*
Disc. (papers 24—25): B. Vahlquist.
26. Alfred Sundal, Norway: *Osteopetrosis. Clinical and Postmortem Examination of a Case.*
27. Rolf Zetterström, Sweden: *Metabolic Disturbances in the Skeleton in Rickets.*

28. Bertil Lindquist, Sweden: *Effect of Vitamin D on the Metabolism of Radiocalcium in Rachitic Rats.*
Disc. (papers 27—28): C. E. Räihä.
29. Ib Boesen, Denmark, and S. Vendel, Sweden: *Type Distribution in Cong. Malformation of the Heart in Early Life (0—3 years) Compared with the Abbott 1 000 Patient Group.*
Disc.: E. Mannheimer, J.Lind and C. Wegelius, S. Vendel.
30. Alf Ödegård, Norway: *Judgement of the Growth of Children with a Diagram, after a "Grid-method".*
Disc.: W. Olsson, P. Karlberg.
31. Annelise Dupont, Denmark: *On the Occurrence of Escherichia Coli 55: B5: 6 and E. coli 111: B4 in Fæcal Samples from Infants with Diarrhœal Disease, and in a Control Material.*
Disc.: J. Grönroos.

Section V

Saturday, June 16th, 9 a. m.—12 a. m.

Prof. C. Gyllenswärd took the chair.

32. Niilo Hallman, Finland: *On Calcium Metabolism in Interstitial Plasma Cell Pneumonia in Infants.*
33. Rolf Reiler, Norway: *Pneumonia Therapy at the Ullevål Hospital during the Year 1949/1950.*
Disc.: C. Friderichsen, Y. Åkerrén.
34. Sverre Hestetun, Norway: *Late Sequelæ of Hemophilus Influenzæ Meningitis.*
Disc.: B. Hahn.
35. Ole Wasz-Höckert, Finland: *The Results of the Treatment of Tuberculous Meningitis of the Children's Clinic, Helsingfors.*
Disc.: K.-A. Melin, G. Herlitz, A. Kåss, O. Wasz-Höckert.
36. H. Enell, Chr. Lingen, K.-A. Melin and S. Hedman, Sweden: *The Influence of Various Remedies upon Tubercle Bacilli.*
37. L. Hesselvik and B. Vahlquist, Sweden: *Triple Vaccination in Infancy.*
38. Bengt Jonsson, Sweden: *The Treatment of Acute Rheumatic Fever with ACTH and Cortisone.*
Disc.: K.-H. Karlén, R. Rinvik, T. Salmi, J. Vesterdahl.
39. Hilkka Tähkä, Finland: *On Influence of Epinephrine and ACTH on the Eosinophil Count of Blood in Severe Infantile Gastroenteritis.*

40. Zaida Eriksson-Lihr, Finland: *The Function of the Suprarenal Cortex in Allergic Diseases.*
Disc. (papers 39—40): J. Ugland, C. E. Räihä, H. Tähkä, B. Hellström, L. Salomonsen, J. Vesterdahl.
41. O. Pettay, Finland: *Preliminary Investigations of in Vitro Leucocytolysis in Allergy.*

Section VI

Saturday, June 16th, 3.45 p. m.—5 p. m.
Prof. L. Salomonsen took the chair.

42. Roald Rinvik, Norway: *Precocious Puberty Granulosa-cell Tumor.*
Disc.: Y. Åkerrén.
43. H. Hagelsteen and O. Skaug, Norway: *An Investigation on the Absorption and Excretion of Radioiodine in a Material of Healthy and Diseased Children.*
Disc.: M. d'Avignon.
44. Bjarne Andersen, Norway: *Acrodynia Caused by Exposure to Mercury.*
45. Erik Jacobsson and Herman Gladnikoff, Sweden: *Hyaluronidase as an Agent Facilitating Intramuscular Urography in Children.*
46. C. A. Hernberg and P.-E. Heikel, Finland: *The Skeletal Age in Diabetic Children.*

PRESIDENTIAL ADDRESS AT THE TENTH NORTHERN PEDIATRIC CONGRESS

On behalf of the Swedish Committee of the Congress I heartily welcome the pediatricians from the five Nordic Countries to the Tenth Northern Pediatric Congress. We Swedes are delighted to see so many colleagues from our neighbouring countries, and are grateful for the many promises of active cooperation in the form of reports, addresses and contributions to the discussions. Our special greetings are due to the guests whom we have the honour and pleasure of seeing amongst us today, particularly the representatives of our countries' Legations in Stockholm and to Doctor Axel Höjer, Director General of the Swedish Royal Medical Board, who have kindly consented to honour the Congress by their presence. I would also specially welcome the only Honorary Member present, Professor Wilhelm Wernstedt.

At the Congress in Copenhagen 3 years ago Professor Adolf Lichtenstein was elected President of the Congress which opens today. He was pleased to accept this task, as were the Nordic pediatricians that he should be their President. They knew that the Congress would have every likelihood of success under his wise and experienced leadership. They were glad to be able to pay this honour to Lichtenstein for all the great contributions he had made as pediatrician and as one of the mainsprings of medical cooperation in Scandinavia. But fate willed otherwise. On the way to the International Pediatric Congress in Zürich in July last year he fell suddenly ill. He was forced to break off his journey and immediately return to Stockholm, where he died a few days later, on July 21st.

Lichtenstein's death has meant a severe loss to Swedish pediatrics. He had, to be sure, already reached the age of retirement which to him, however, was not an opportunity for well-deserved rest after a full life's work, but rather a chance for the concentration of and of a new marshalling of his powers upon the tasks for which his onerous and exacting post as a University Teacher had allowed him no time. His scientific production, far from flagging, was becoming more intense. I think that we, who knew Lichtenstein's

enthusiasm for scientific work, his ingenious mind, his fixity of purpose and indefatigable energy in carrying a task to its conclusion, were sure that we could still expect many valuable contributions from his own hand or inspired by his leadership.

Lichtenstein's scientific studies are well known by pediatricians in our countries, and cannot of course be the object of evaluation on this occasion. I would merely mention that his most important scientific achievements have been in the realm of diseases of the blood, infectious diseases and diabetic problems. These three fields of research to some extent mark three stages in his scientific activity, allied as they are to the hospitals at which his work lay at the time: first the Sachs' Children's Hospital, then the Epidemic Hospital and finally Crown Princess Lovisa's Children's Hospital. Being the leader he was, his influence was naturally felt by his co-workers and disciples and extended to their scientific work. He gave them all the support and encouragement they needed and stimulated them to do their best.

One of his more important contributions to the development of the care and medical treatment of children in our country was the establishment of children's departments at the County Hospitals. This was an aim for which he continued for many years to propagate verbally and in his writings, and which has already to a great degree been realised. Another of his measures that has borne fruit was the plea for closer cooperation between obstetricians and pediatricians in the care of new-born children, and for the employment of pediatricians as consultants at our maternity hospitals. The terms of employment of pediatricians lay close to his heart. The initiative in the formation of the Swedish Childrens Doctors Association was his, and for 10 years he was its President. In this capacity he performed a work of paramount importance towards improving the status and conditions of employment of children's doctors. I should imagine that the work of Adolf Lichtenstein in this respect had a certain influence on developments in the other Nordic countries as well.

Adolf Lichtenstein was always deeply interested in medical cooperation between the Nordic countries, and particularly in the sphere of pediatrics. "Acta Pædiatrica", which was started after the First Pediatric Congress in 1919, and which has played so important a role in collecting the results of Nordic pediatric research within one journal, has from its birth found a warm supporter in Adolf

Lichtenstein. He was from the beginning a member of its Editorial Staff, and its Chief Editor from 1946 until his death. He was also for 20 years one of the mainstays of and a loyal and unselfish collaborator in "Nordisk Medicin". This journal originated as an expression of the demand for independence, the need of emancipation from foreign influence, and the desire to gather together all our medical production under the Nordic colors. Te publication of "The Nordic Text-book of Pediatrics" (Nordisk Lärobok i Pediatrik) was quite certainly inspired by similar thoughts and feelings. Its first edition was published by Adolf Lichtenstein, Sven Monrad and Theodor Frölich. The second edition of the Text-book, published in 1943, was the work of Adolf Lichtenstein alone.

Lichtenstein has taken part in all previous Nordic Congresses as an active member. His remarkable powers of expression and immense knowledge made him an outstanding personality who always commanded attention. He had shared in the work of preparing all the Nordic Congresses hitherto, both as a member of the Swedish Section of the Nordic Pediatric Association and for a number of years as its Secretary.

Strong of will, upright, independent, unafraid, a lover of justice and unusually honest, loyal to everything that he valued — that is the picture given of him by one of his biographers, Professor Gunnar Holmgren, and it is the picture of Adolf Lichtenstein that we shall always remember.

Swedish pediatrics has suffered yet another severe loss. On June 4th this year the sorrowful news was announced in Stockholm that the Head of the Sachs' Children's Hospital, Henning Magnusson, had suddenly left us for all time. He fell at his post, while doing his normal rounds in his beloved hospital. The news of his death was not altogether unexpected by his family and closest friends, who were well aware of his failing health and realised, as did he himself what might take place at any moment.

In Magnusson a great clinician and successful scientist, and a widely respected and beloved physician has passed on — humanly speaking all too early — at the age of only 47. He was one of that group of capable and successful pediatricians of the intermediate generation who have held the banner of pediatrics high in Sweden, and who in no small degree have helped to bring the art of treatment of children's diseases in Sweden to its present high level. His education was gained under Jundell and Wernstedt at the Nortull

Hospital. He later completed his pediatric training by studies in epidemiology and on foreign travels. He returned to Norrtull Hospital as head of the outpatient department and was thereafter Professor pro tem. for 2 of the 5 years of interregnum after Wernstedt's departure. In 1944 he was appointed Chief Physician at the Sachs' Children's Hospital. In this position it was his fortune to take part in designing the rebuilding of the hospital, a task which greatly appealed to Magnusson and to the solution of which he devoted immense effort. The result has been an outstanding success. I think that the buildings added to the Sachs' Children's Hospital can without exaggeration be said to have made it one of the finest and most modern children's hospitals in Sweden.

Magnusson's scientific production had already grown to considerable proportions during his period as House Physician. His bent for research burst into full bloom when in 1944 he took over the leadership of the Sach's Children's Hospital, where he was succesful in gradually gathering and welding together a group of young and energetic co-workers in research. Among the more significant of the works published by Magnusson I would particularly mention the thesis on the blood picture of premature infants, the poliomyelitis studies, his investigations of toxoplasmosis, his presentation of and experiments with tuberculin BCG, his inspired attempts to combat mosocomial infections, his clinical investigations of the value of amino-acids in the feeding of prematurely born children. Magnusson had a peculiar gift of making contacts of value to his work with scientists in different spheres, especially biochemistry, bacteriology and virology, by which his production was greatly enriched. His scientific work has the stamp of reliability, clarity and good judgement.

At the time of his death Magnusson was Chairman of the Section of Pediatrics and School Hygiene of the Swedish Medical Association, a task which in his characteristic fashion and in spite of his delicate health he undertook and performed with great credit and with a high sense of duty.

Magnusson was a considerate and kindly person, who quietly went on his way, careful to avoid unnecessary stumblingblocks and to shun any grounds of strife or bitterness. He was a man of peace, one of those rare and noble characters who sacrifice all for their patients, are loyal to their colleagues, a gentleman and a credit to the Swedish medical profession.

Norway too has lost one of her more notable pediatric members; on July 12th, 1949, Dr Kirsten Utheim-Toverud died while on a visit to the United States, where she had been for 6 months with the whole of her family. At her death she was 59 years old. After training at different departments in Oslo, including a period at Frölichs' Children's Clinic, and at hospitals and laboratories in Copenhagen and Berlin, she undertook a study tour of the United States in 1919. This visit was to last 4 years, in which time she advanced to the position of Assistant Lecturer in Pediatrics at the St. Louis Clinic. On her return to Norway in 1923 she was created Doctor of Medicine on the strength of a thesis on nutritional disorders in infants. In the same year she was appointed House Physician at the Children's Department of the National Hospital (Rikshospitalet).

For many years Kirsten Utheim-Toverud was a very productive scientific author, whose name often appeared in Scandinavian and American journals. The majority and the most important of her works deal with social-pediatric problems or questions closely allied to this field. She started there on a line of research, which early awakened international attention, and the results of which are often quoted. Her studies were conducted at health centres under her charge, homes for children and mothers among which was a home for diabetic children. In a series of works she dealt with infant nutrition, the importance, for the infant's health, of the mother's diet during pregnancy, and various diabetic problems. In conjunction with her husband, G. Toverud, Professor of Odontology, she also devoted her attention to preventive dental hygiene.

Utheim-Toverud had a lively interest in social questions, played an energetic part in the spread of general enlightenment, and produced a number of popular publications on medicine. There is no doubt that her achievements in the sphere of social hygiene went far towards creating a better understanding throughout the Nordic countries of the importance of a right diet for mother and child. She impressed you with her personality, her clear intellect and thorough knowledge of the spheres that were the object of her interest. She was friendly, though little distant and reserved, despite which she made numerous friends among colleagues and laymen, by whom she was held in high esteem. A rich and active life in pediatrics in its widest sense, come to a close in the death of Kirsten

Utheim-Toverud. Her departure signifies a deep loss to Norwegian pediatrics and child welfare.

On February 13th last year the Finnish pediatrician Einar Rafael Nystén died at the age of 68. His activities were centred at the Helsingfors Epidemic Hospital, where he held a post as Physician from 1915 until his retirement. During that time he published a number of works on serology and bacteriology. He was a member of the Nordic Pediatric Association and was a welcome guest at our Congresses. He was a sound physician and a steadfast friend.

I will now ask the audience to rise for a minute's silence to honour the memory of our four departed colleagues and friends.

At our Congress this year we are also sorry to be without some of our Nordic colleagues, who on account of illness or for other reasons have been unable to come. Among them are two Honorary Members, Professor Bloch of Copenhagen and Professor af Klercker of Lund, also Dr Rothe-Meyer of Copenhagen and Dr Stoltenberg of Oslo. I would propose to the Congress that we cable our greetings to these absent colleagues.

Now for the tenth time Nordic pediatricians are gathered in a Congress. It is perhaps an occasion to cast our thoughts back to and revive the memory of the nine previous Congresses. A glance at the printed records shows that the programs provide an accurate reflection of the advance of pediatrics and of the changes in the field of pediatric work during the last third of a century in the Nordic Countries.

At the first two Congresses shortly after the first World War discussions were still revolving around the acute and chronic nutritional disorders in infants. The theories that were being advanced were at that time the almost essential, or at any rate the most complicated, part of pediatric teaching. To medical students of today nutritional disorders are no longer hardly a difficult problem. They have practically disappeared with the improvement in standards of living, the increase in popular knowledge and preventive child welfare. Rickets and spasmophilia have gone the same way. At the first three Congresses these diseases were given a prominent position, and at the Third they formed the main subject of discussion. They are now so rare that, at least as far as Stockholm is concerned, there is no opportunity from one group of medical students to another of demonstrating typical and pronounced cases

of rickets. At the Third Congress insulin treatment of diabetes also came up for the first time and subsequently remained on the program for about 15 years. Tuberculosis was also a favourite theme and formed the main subject at the Fifth Congress in 1931. At the following Congress, in 1934, the nosocomial infections were to the fore, due to their frequency and the interruption they caused in the hospital treatment of pediatric cases. These infections have admittedly not disappeared, but they seem to have far less significance now than they did 20 years ago. We have better isolation arrangements, staffs have more understanding of protection against infection, the time of hospital treatment is far shorter, and last but not least — the new chemo-therapeutic and antibiotic preparations have helped us to master these diseases. It was not until the Eighth Congress in 1946 that sulphonamide treatment appeared on the programme, and at the Ninth, in 1948, antibiotics.

There is no doubt that the task of pediatricians has changed during the past years. The more the somatic, preventable diseases have decreased and disappeared, the more other disorders and pediatric problems that have previously remained in the background have come to the fore. Among these are social-pediatric problems and mental disorders in children. The former have been on the programs of recent Congresses, and this year psychosomatic medicine is the chief subject. That there is interest for the introduction of new methods of examination is exemplified in the congenital diseases of the heart, which also show that improved methods of examination open the way to hitherto unknown therapeutic action.

Just as earlier Congresses gave quite a true picture of the changing interests of pediatricians during those years, the programme of this year's Congress reflects the present interest, composed as it is of experiences of prevalent diseases, of studies that have been made possible by new examination methods and by up-to-date therapeutic measures. The very lively pediatric research that is at present being conducted in the Nordic countries is also typified in the program. The number of contributions sent in filled the Congress program to nigh the bursting point. The idea from the Copenhagen Congress of limiting the length of open contributions to 10 minutes has been gratefully followed by us. We shall stick rigidly to that limitation. We should nevertheless have been unable to get through all the contributions and reports that have been

accepted, had we not given part of the program in the form of a scientific exhibition. This has been made possible by the great generosity of certain commercial and industrial exhibiting firms. I take this opportunity of expressing our hearty thanks to the representatives of those firms who are present for the assistance they have thereby given to pediatric research.

In the hope that this Congress will worthily follow in the steps of its predecessors, that it will be scientifically profitable and of value to our profession, and finally that our meeting together may be accompanied by enjoyment, I herewith declare the Tenth Northern Pediatric Congress opened.

Psychosomatic Disorders in Pediatric

by

SVEN AHNSJÖ, *Sweden*

The authors Weiss and English mean in their book "Psychosomatic Medicine" that this term really should not be used because "good medicine will be psychosomatic". The authors are of course quite right and they hope for a future when this term is no more necessary. Psychosomatic pediatrics is perhaps already a term, which for many children doctors seems to be an unnecessary attachment to pediatrics. We should perhaps be inclined to assume a priori that children doctors more than other physicians are and have been adjusted to the fact that psychic factors play a part on the genesis of physical diseases. Pediatricians are indeed often in situations, that give them many direct opportunities to observe, for example, different forms of feeding rejection, children who vomit from aversion to school and on the whole to everything that develops during affect situations, where we observe a whole series of physical symptoms, even convulsions and unconsciousness.

The physical effects of emotions, the effects of sorrow, shyness, fright and anxiety are easily studied in children too.

In spite of that, experiences during last few years have clearly shown, that this special field of medicine and pediatric is able to defend its exceptional position, by the way, in which it has tried to explain different problems. From different angles, more and more clearly, it has been shown through intensive research that more numerous physical symptoms and diseases, for which a somatic character was assumed to be indisputable, are dependent on psychic factors; psychogenic stimuli for their source and development. That field of science, which has taken as its objective the investigation the role psychic factors play in the genesis of physical symptoms and diseases, has been called psychosomatic medicine.

If one tries to evaluate what has been done in this field, he finds important contributions from all over the whole world, but sometimes contradictions, which interferes with the possibility of getting solid knowledge and survey.

The scientific work follows two lines, the physiological, making use of modern laboratory methods and animal experiments, and the psychological, where the psychoanalysis (deep psychology) plays an important part.

In the physiology the interest sometimes has been concentrated upon the studies of hormones and sometimes upon the studies of the vegetative system, in every case upon that mechanism, which regulates the "milieu intérieur" (Claude Bernard) with the hypothalamus and the hypophysis as central organs in contact with higher and lower centers. The American, Cannon, invented the term homeostasis to express the ability of body to preserve its state in spite of different strains. He, and his followers, pointed out the importance of the autonomic nervous system in that function. Example on situations, by which this function is strained and gives way, have been given by several scientists, such as Pavlov and Messerman. The modern so called science of stress created by Selye in Canada is based in part on the observations made by Cannon and his work must now be considered fundamental to psychosomatic science.

I do not intend to give great detail about these scientific investigations. A short summary will soon be published by S. Wohlfahrt in Svenska Läkartidningen. Here only some of the most important principals will be reported. The organism responds with different reactions to stimuli, at first hand with an alarm reaction, but under continued pressure a state of resistance or if the defense sags a stage of exhaustion ensues. The first alarm reactions are nonspecific and are of two different types, shock and counter-shock type, the former resulting from the injury or damage and the latter being an active reaction of defense. The resistance of the body decreases during the shock and is increased above the normal during the counter-shock. The early active steps of defense seem to be production of hormones (adrenaline from the suprarenal cortex, ACTH from the anterior lobe of the hypophysis etc.) resulting in elevation of the blood-pressure, in tachycardia, in an increased blood-sugar, and in an increased number of neutrophils together with decreases in the lymphocyts and eosinophils.

The following state of resistance is characterized by a rise of the specific resistance against the exciting agents while the resistance against other agents may decrease.

Of special interest are the animal experiments in which Selye and his pupils have reproduced stress changes, by the administration, over a long time, large doses of suprarenal cortical hormone or by psychical strain, such as lesions of the kidney, damage to blood vessels, gastro-intestinal ulcers etc., effects which may be compared to the different forms of wear and tear diseases of the human body.

It is here, of course, that the connection with the psychosomatic diseases of different types will be obvious, situations where the stress, the psychic strain plays an important part. As, for example, in the neuroses of war, we must imagine that a chronic affective strain or tension, produced by a variety of conflict generated agents, keeps up an overproduction of hormones, which is ultimately injurous to the body, and finally results in an exhaustion state. Some animal experiments tell us that these reactions are related primarily to the hormones from the suprarenal cortex, as illustrated by the investigations of Richter with rats, in which the stress increased the suprarenal cortex and the opposite situation diminished or even led to atrophy of the same substance. Of interest in this connection is what the Swedish psychiatrist Gadelius in the year 1921 says about the possibility of the psychic genesis of hyperthyroidism. He tells how he and others thought that psychic stress may give rise to the symptoms we observe in those patients and that the enlargement of the thyreoid may be a result, building up a vicious cycle.

The treatment of neuroses and psychoses during the stage of exhaustion with extracts of the suprarenal cortex and ACTH has not as yet given any sure results. In pediatrics such therapy has scarcely been tried and the psychiatric aspects of stress science are only in a beginning phase.

Beside this physiological and animal experimental research the psychological has more and more been of interest; that is the science, through which tries to be explained the action of those agencies which may be supposed to have given rise to conflicts, which have formed a situation leading to somatic disorders or disturbances.

Sound practice in psychosomatic medicine is to be contrasted with the old, and yet too common, attitude of establishing a psychogenetic cause for a disturbance without more closely analysing the

situation and obtaining for the patient, an understanding of the problem, in other words, against the common practice of many doctors of telling the patient that his symptoms are nervous, be of consoling parents with the information that the symptoms will disappear with time. Instead, psychosomatic medicine is intent upon the possibility of bringing out the direct psychogenetic factors and of delivering the patients from their influence and possible bodily harm. Recent knowledge about the neuroses has given to psychosomatic medicine the possibility of understanding that the primary causes are more closely related to the psychopathology of the personality than to the pathology of the organs. When both psychic and somatic factors are active the question becomes, how much one and how much the other factor mean, and how the two factors are related to each other.

It is inescapable that psychoanalysis more than anything else has given us the knowledge about the factors which we have to deal with in the psychopathology of the personality, it has shown how, even early in preschool age, the psychical disturbances are seeded and how they may be actualized at puberty etc. It has been determined that anxiety has a specific unfavourable action in stress situations especially anxiety in the form of desperate degrees of insecurity at different periods of life as a lack of satisfying human contact, even during the first year of life. Later child may meet the same threat of loss of security, either in conflicts in the family life or in other interpersonal relationships. We need to pay attention to the importance of those strain moments, which are active for a long time and to the way in which somatic symptoms appear, or turn up, when the usual opportunities to obtain an adequate outlet for emotions are not available. Many authors Freud, Alexander, Menninger, French, Miller, Deutsch, Saul etc. have expressed this view.

In Sweden we have some authors, who have studied this problem in children, such as Nycander, who showed the connection between inhibited aggressions on one side and anxiety on the other, defective contact and the appearance of several psychosomatic symptoms, especially in boys. The connection between states of aggression and psychosomatic symptoms has also been studied by Siv Gunnarsson in children suffering from asthma. Half of her patients were obviously inhibited in their aggressions and their attacks usually appeared at the same time as inhibitions.

Individual constitutional factors determine largely which symptom will be brought out, but it is not necessary to go into that aspect here.

The diagnostic methods by which psychosomatic disorders are studied will be discussed by others, especially in regard to the place of psychic observations in the study of real somatic cases.

The treatment, from psychological point of view, must generally be in the form of a reeducation of the individual, giving a more permanent balance to the different parts of the personality. Such a balance cannot be realized through volontary actions on the patient's part, on the contrary, it is possible only if the emotional conflicts of the person can be neutralized and be given a more favourable emotional sphere in which to develop. Often this means an attempt to get a release from, and a more adequate meeting of, such feelings of anxiety and unsecurity, which have inhibited the person and paralysed his activity.

In more manifest and advanced psychosomatic disorders the treatment ought to be directed along lines which have been drawn up by polydimensional diagnostic procedures. A team consisting of individuals trained in medical, social and psychological techniques is in many cases essential.

It cannot be denied that in the eagerness to find the deepest source of conflicts, of that kind, which here comes into consideration, exaggerations occur which seem to be beyond the borders of common sense, but we should not stop further development through an ungrounded scepticism in relation to the most important experiences. The author wishes, primarily, to consider the experiences of the importance, in a proper study regarding the development of psychosomatic disorders; in other words, the importance of that stress, which children are subjected to, when they are prevented from giving expression to their emotions and are obliged to live in anxiety and unsecurity.

It is important to point out the causes of those symptoms, which are the first signs of a more or less chronic stress upon the individual, situations which are commonly satisfied by drawing attention to the existence of a psychic genesis. This may be especially important for doctors, in general practice, at children stations and in schools.

Here one deals with many everyday problems. Loss of appetite, and rejection of feedings may have as their cause an anxiety state

grounded on the lack of understanding of or interest in the child on the part of the mother. It is also possible that nightmares, impulsive aggressiveness and motor restlessness, stuttering, tics etc. may originate in an anxiety, which must be allayed to achieve improvement and where the possibility of accomplishment may be greater than is at first thought. If we try to search for the causes of the child's anxiety, we generally succeed even if we cannot get to the fundamental reason for it. It is essential to eliminate the unsecurity and anxiety before one can obtain a deeper influence. No child should have to suffer for a long time from such disturbances as nightmares, for example. The necessary treatment ought to be known to every doctor. This is so much more important than many neurotic symptoms in childhood, which appear later on in life, such as truancy, untruthfulness, stealing etc., which have the same genesis whether they are connected with somatic antecedents or not. It is desirable to give medical students such instructions teaching that they are in the future able to be active workers in this field of mental health.

There are many forms of psychotherapy and every doctor must master the most fundamental of these. All cases need not and cannot get psychoanalysis, but the study and the treatment of the patient, as well as the prophylaxis must, I think, follow a parallel direction. Several psychosomatic diseases may then be eliminated. The most common of the more severe diseases of psychosomatic nature in childhood have been or will be discussed by other speakers. In these groups such as asthma, ulcerative colitis, migraine, skin disorders, and some metabolic disturbances individual experiences indicate a connection with psychic factors, but the picture is complicated by other factors, allergic, hormonal etc., which make it difficult to draw definite general conclusions. No group of studies free from objections and developed from the observation of comparable cases with and without psychological treatment, have yet been published. The need of psychotherapy as well as somatic therapy appears to be indicated, in spite of this short coming, in most cases, where anxiety, unsecurity and loss of self-confidence are as a rule associated with the syndrome and where the difficulty may be caused, or accentuated, by different psychological factors, such as exaggerated care and attention from the parents or hostility, or other forms of disturbed relationship. Klackenberg (1948) gave a short survey illustrated with some own cases. He discussed the psychogenic

factors in herpes zoster. Some skin disorders may be very obvious examples of psychic genesis in spite of having a connection with infectious and allergic factors.

In some psychosomatic disturbances there is a great sensitivity to the psychic agents. Everyone may have some experience with nocturnal enuresis. There we also have a complexity of active factors, and everybody knows how a change in the factors may modify the situation. In childrens' homes we can study how an agitated state increases the frequency and how a quieter situation decreases the frequency. We know too, how very simple methods, when they give a higher self-confidence and more security, sometimes stop an enuresis at once.

To illustrate this sensitivity I want to give the results from observations on the frequency of enuresis according to the different days in the week. The observations were made at a children's home during the years 1946—1950. There were 100 boys and 39 girls, aged 3—13 years, who were for a shorter and longer time at the reception and observation home, Nybodahemmet, belonging to the Child Welfare Board of Stockholm.

From Diagram I and Table 1 it is to be seen how the frequency varies, both with girls and boys, in such a way that it decreases the night before Friday, Saturday and Sunday and especially the night before Monday, and it then rises and remains on a high plateau for the rest of the week. The great decrease the night before Monday is also shown in Diagram II, where as in Table 1, the distribution is arranged to compare the children over and below the age of seven. In both groups and in both sexes the decrease is the same. The investigation has been completed with calculations giving the frequency of enuresis during Easter-, Christmas- and summertime compared with the frequences of enuresis in the same children other parts of the year. Table 2 shows how the frequency decreases, even if this decrease is not so large, and the result is not significant in statistical sense. As might be supposed, children had visits from or visited their relatives on Sundays and because of this their feeling of security had risen the nights after Sunday. Those children who did not have any visits were investigated alone, and Diagram III and Table 3 show their reactions, with the same tendency as the whole material.

Food and medicine don't influence the situation and the author has not been able to find any other explanation of these variations

Table 1

The frequency of enuresis nocturna in boys and girls distributed over the ages before and after seven years

(S, M, T, W, Th, F, Sa = Sunday—Saturday)

Sex	Number of children	Age		Number observed nights	% wet nights of all nights to						
		between	average		S	M	T	W	Th	F	Sa
♂	47	3 : 3—6 : 11	5,10	622—643	58,4 ± 1,96	47,0 ± 1,99	61,1 ± 1,92	67,0 ± 1,86	68,9 ± 1,84	57,2 ± 1,96	66,0 ± 2,16
♂	53	7 : 0—12 : 1	8,90	676—697	50,6 ± 1,92	45,9 ± 1,91	54,8 ± 1,90	56,8 ± 1,89	59,4 ± 1,86	54,7 ± 1,88	55,4 ± 1,90
♂	100	3 : 3—12 : 1	7,12	1308—1332	54,3 ± 1,38	46,4 ± 1,38	57,8 ± 1,35	61,8 ± 1,33	63,9 ± 1,32	55,8 ± 1,36	56,0 ± 1,37
♀	24	3 : 1—6 : 11	5,15	422—435	63,1 ± 2,32	50,3 ± 2,41	69,6 ± 2,21	68,5 ± 2,22	71,7 ± 2,17	64,6 ± 2,30	67,3 ± 2,28
♀	15	7 : 4—12 : 7	9,18	140—143	45,0 ± 4,20	34,7 ± 4,01	56,6 ± 4,15	49,6 ± 4,21	50,3 ± 4,19	51,7 ± 4,18	51,7 ± 4,18
♀	39	3 : 1—12 : 7	6,71	571—577	58,7 ± 2,06	46,6 ± 2,09	66,4 ± 1,97	63,9 ± 2,00	66,4 ± 1,97	61,4 ± 2,03	63,4 ± 2,01
♂ + ♀	139	3 : 1—12 : 7	7,00	1876—1908	55,7 ± 1,14	46,5 ± 1,15	60,4 ± 1,12	62,4 ± 1,11	64,7 ± 1,09	58,3 ± 1,13	58,2 ± 1,14

Table 2

The frequency of enuresis nocturna at Easter-, Christmas- and summertime compared with the frequency during the rest of the year by the same children

Yeartime	Number of children ♂+♀=♂+♀	Number observed nights	% wet nights of all obs.	Difference Easter—Not Easter etc.
Easter	25+ 9=34	216	55,8±3,3	−3,9±3,3
Not Easter	25+ 9=34	4793	59,7−0,7	
Christmas	27+ 9=36	569	62,4±2,0	−1,9±2,1
Not Christmas	27+ 9=36	4671	64,3±0,7	
Summer	33+14=47	1560	54,0±1,2	−3,0±1,4
Not summer	33+14=47	4991	57,0±0,7	

Table 3

The frequency of enuresis nocturna the nights before different days in the week in children, who never get visits compared with the frequency by all enuretic children in the material

(S, M, T, W, Th, F, Sa = Sunday—Saturday)

Material	Number observed nights	% wet nights of all nights to							The standard error varies between
		S	M	T	W	Th	F	Sa	
No visits	52—57	55,8	50,0	63,0	71,4	80,7	61,4	61,8	±5,2 —±6,9
All children	1876—1908	55,7	46,5	60,4	62,4	64,7	58,3	58,2	±1,09—±1,15

than that, which lies in the Sunday itself and which has a correspondence with Christmas and Easter as a holiday and which differ in some degree from the summer and other parts of the year, that which adult persons feel in the relaxing of the tension and stress in everyday life.

Even if such things are to be listed as psychosomatic disorders, how many influences are there which are responsible for symptoms of this kind? We must understand the importance of delivering the patient from anxiety and insecurity.

Diagram I

The frequency of enuresis nocturna in boys and girls the night before different days in the week. Compare Table 1

(S, M, T, W, Th, F, Sa = Sunday—Saturday)

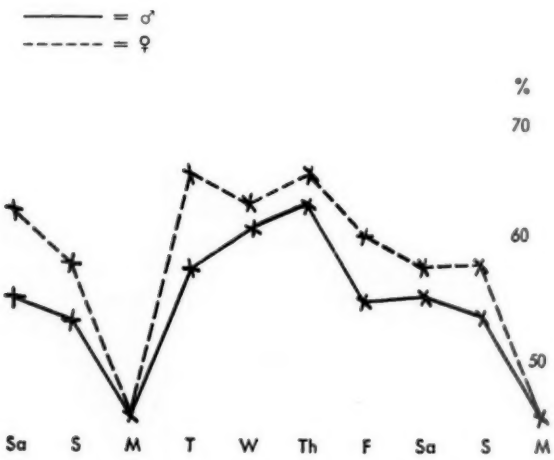


Diagram II

The frequency of enuresis nocturna in boys and girls above and under seven years the nigth before the different days in the week. Compare Table 1

(S, M, T, W, Th, F, Sa = Sunday—Saturday)

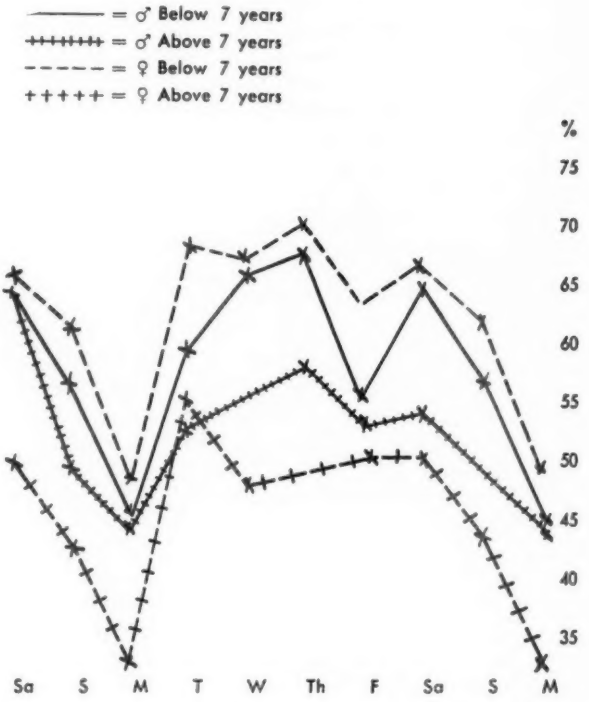
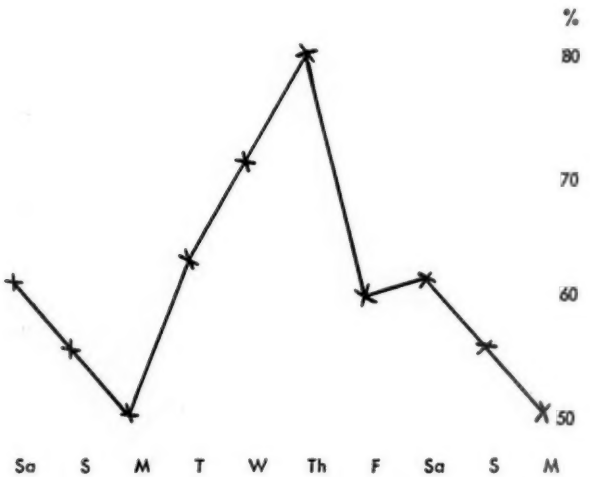


Diagram III

The frequency of enuresis nocturna in those children (boys and girls), who never get visits. Compare Table 3

(S, M, T, W, Th, F, Sa = Sunday—Saturday)



Psychosomatic Disease in Childhood

by

OLUF ANDERSEN, *Denmark*

The present generation of doctors realizes to a greater extent than ever before the significance of the psychic factor in a number of morbid phenomena.

A relation between psychic affections and organic symptoms has been demonstrated in many fields, with the result that efforts are made in individual cases to get to the core of the matter and try to find the psychic cause and treat it. By this it should not be understood, of course, that we are on the threshold of anything epoch-making or new in medicine; the good physician has always realized that he must treat the patient from a psychic point of view whilst at the same time dealing with the physical symptoms. The doctor has always exerted great influence on the psychic condition of his patient, throught conversation with the patient, by the attitude to the patient's problems which he adopts, and not least by the treatment he proposes.

It is worthy of note that the two factors of particular significance in the relation of doctor to patient are, firstly, the great importance to the patient of being able to talk fully to the doctor about his problems, and, secondly, the suggestive influence exerted when the doctor institutes treatment of some kind. These two factors are part of all medical art, and also, by the way, part of the quack doctor's art, but they are of the greatest significance nowadays in our dealings with psychosomatic affections.

As mentioned before, it cannot be said that we are facing any new creation in medicine when we talk about psychosomatic affections. It is only that the physician has become more aware of his task. He can see clearer than before the reciprocity between the psychic and the somatic, and thus he brings the psychic factor somewhat to the foreground — sometimes, in fact, so much that it almost looks as though he forgets the somatic side of the condition.

There is probably nothing surprising in this fact, which must be interpreted as a reaction against the rationalistic attitude prevalent in some medical circles, particularly in the University, at the beginning of this century. This attitude followed in the wake of

technical, physical and chemical progress in medicine which occupied some doctors so much that they almost forgot the patient's person in the intellectual joy of being able to establish the existence of a disease and make a diagnosis by means of test tube and the apparatus of chemistry and physics. It often went so far that if nothing abnormal could be demonstrated by such examination methods, it was assumed that there could be nothing at all wrong with the patient. The only thing to be done in such a case was to shrug the shoulders contemptuously and make a diagnosis of presumed neurasthenia.

It is difficult, from a purely academic point of view, to select a certain group of affections and define them as psychosomatic, because almost all diseases are psychosomatic. Every physical disease is accompanied by psychic symptoms, and every psychic affection as a rule gives physical symptoms.

Nevertheless, the reason why efforts have been made to try to select certain groups of diseases and designate them psychosomatic is because it has been established in recent times that unfavourable living conditions often result in psychic disturbances in conjunction with physical symptoms. Thus it is the factor "living conditions" — environment — one has to bear in mind when talking of psychosomatic affections.

When trying to ascertain the basis on which a psychosomatic symptom complex rests, one tries, therefore, to find the possible cause in the conditions under wich the child lives; one looks for environmental factors. If such can be found we speak of "environmental damage". It must be emphasized, however, that also the physical and mental constitution of the patient is of significance in considering the disease picture one finds.

Here we will examine the question of environmental damage and speak later of the role of the constitution.

We can divide environmental damage into (i) psychic and (ii) somatic.

Psychic environmental damage occurs as the result of "broken homes", divorce, jealousy of brothers and sisters, school difficulties, bad social conditions, unsatisfactory housing conditions such as overcrowding, etc. The reactions to such conditions can be very varied, sometimes taking the form af purely nervous symptoms such as tic, enuresis, bad behaviour, etc., but also purely somatic symptoms can be the result, e. g. stomach pains, headache, unsatisfactory

growth and sickly ill-looking children, in other words children who can be included in the category "deficient children".

Somatic environmental damage can result from bad social conditions, unhealthy housing, deficient nourishment, insufficient sleep, too much work, infection from those around, etc., but it can also occur in higher social spheres as the result of bad eating habits and other unhygienic factors. In these circumstances one can find exactly the same disease picture as for children from mentally insecure environments. The children may be tired, sickly, unbalanced or badly behaved, and often somatic complaints such as headache, stomach pains, etc. occur. Various somatic affections such as anæmia, tonsillitis, sinuitis, vegetationes adenoidæ, streptococcus infection, digestion troubles, etc. can also be found.

In all these cases it is a question of chronically sick children whose nervous symptoms occur because they are ill. All can be included in the "deficient children" category.

We can see, therefore, that the "dificient children" group includes two different categories of children. Ooutwardly, i. e. in physical appearance, there need not necessarily be any difference between the two groups. The difference lies solely in the way the deficiencies have arisen; as regards the first group the origin of the symptoms is unfavourable psychic influences, and in the second group physical disease.

However, it must be strongly emphasized that it is only very occasionally one comes across unmixed cases. For instance, patients from unsatisfactory social environments are often affected by both psychic and somatic damage. I mention only these two groups in the "deficient children" category in order to point out that different causes can lead to the same symptom complex, and that it is important to bear in mind that all factors must be carefully taken into consideration.

It is just as ineffective to give a physically frail child psychic treatment only, as it is to give a mentally sick child physical treatment only. There are many examples of children being treated psychically for headache, stomach pains, naughtiness, etc. though the cause of the symptoms is purely physical, and the opposite often occurs too.

Certain environmental damage deserves special mention. I am thinking here of that resulting from the child's own chronic or recidivistic illness. It has been mentioned that chronically ill children

can be difficult, but particular difficulties occur if the child or those around him become engrossed by the disease. Then special environmental damage occurs. For instance, I would mention asthma.

Many asthma attacks start when the child has become sensitive to some allergy or other. Others, such as attacks of asthmatic bronchitis, occur in connection with colds. When the child has had such attacks a certain number of times, in between the genuine attacks he will perhaps have numerous attacks of asthma which must be regarded as being of psychogenic origin, and which can actually be interpreted as some kind of Pawlow reflexes. But it must be stressed that in the majority of cases the asthma attacks are due to purely somatic conditions — i. e. as mentioned, allergy or bronchitis — and that these influences will still be capable of causing genuine attacks in addition to the psychically-determined attacks.

If a child and his relations are particularly unsteady psychically, a chronic asthma condition can develop, partly on a psychic basis. Similar cases can also occur if the child is constantly exposed to the allergy which causes his asthma attacks. In all cases a chronic emphysema develops, so that the condition becomes irreparable because of the somatic changes.

In all events, both in asthmatic children and in the previously mentioned deficient children, there will be somatic and psychic causal factors mixed together.

It would also appear that the acquired mental and physical constitution (phenotype) of chronically sick children is of significance for the physical condition. Similarly the congenital constitution (genotype) may have some influence, though the facts in this connection are difficult to ascertain and therefore the central significance of the constitution can easily be overlooked.

As an example of cases where the constitution is presumably of significance, I would mention enuresis. The many cases seen in families seem to justify the presumption of a constitutional element as contributory factor in the occurrence of the phenomenon. The reason why the constitutional causal factor is not taken more into account is because as a rule the picture is veiled by secondarily-occurring unfavourable environmental conditions. These latter occur because the enuresis symptoms, on account of the inconvenience they cause, affect the patience of those around the child, so that his relatives treat him in such a way that he completely loses self-

confidence. In other words, the environment becomes affected unfavourably by the symptom enuresis, and the unfavourable environment causes the enuresis to continue.

In this connection I do not take into account the cases where enuresis occurs as the result of the environments being primarily unsatisfactory.

We have now mentioned somatic and psychic environmental damage as the cause of somatic or psychic reactions, and have made brief mention of the fact that the constitution — physical and mental, acquired or congenital — is also a factor in the origin of the psychosomatic process.

It will also be evident from what I have said that it can be difficult to sort out the effect of the individual factors in each single case. This fact is of great importance to doctors when making diagnoses.

The case history must be adequate from the point of view of the social, hygienic and family circumstances. Subsequent examination must then determine whether the child has physical affections. Even though all the facts indicate that there is a psychic reason for the child's symptoms, thorough somatic examination should determine whether the child has a somatic affection.

The recording of the psychic history and the examination of the child connected therewith should be carried out by the doctor. There is nothing new in this procedure. As I have already mentioned, the conscientious physician has always paid attention to the psychic factors.

What is new is that even in the most simple cases, questions relating to social and pedagogic factors arise much more frequently.

While the usual cases of nervous disturbance in children are of such a type that the doctor can cope with the problem alone, it is sometimes necessary to seek the assistance of a psychologist for the testing and planning of details. The role of the psychologist in diagnostics in the psychosomatic field corresponds to the assistance which the physician gets from the laboratory doctor in connection with somatic examination. It is the duty of the examining doctor to compare and evaluate the somatic and psychic observations in making the final diagnosis.

As regards treatment, it is important first of all to treat the child's somatic affections. The old proverb "mens sana in corpore sano" still applies.

Then the doctor must try to advise the parents and relatives in an attempt to remove the unfavourable somatic and psychic environmental factors.

In more difficult cases, valuable help can be given by the psychologist and social worker. The worst cases with serious behaviour disturbances and character defects, and even actual psychosis, belong to the child psychiatrist. On the other hand, it is incorrect that the child psychiatrist should be burdened with examination and treatment of quite simple cases.

It might be appropriate, when speaking of treatment, to mention that in dealing with symptoms which have a psychic cause or psychic connection, it is of great value if the physician has a certain suggestive power, and fortunately most doctors have. The mere fact that the doctor institutes treatment has a suggestive influence on the patient. It is a well known fact that any administration of medicine affects the patient suggestively. For example, there are some doctors who can cure a high percentage of enuresis patients by means of some simple medicament or other which another doctor could not use to any advantage. The secret lies in the fact that the doctor himself believes in the treatment, and thus he has a strong suggestive effect — perhaps unconscious — on the patient and those connected with him.

Another example of the influence of suggestive treatment can be seen in the treatment of asthma. If one institutes some therapy or other for this condition, the psychogenic attacks will perhaps disappear and the patient can be free from symptoms for quite a long time — at any rate until he gets his next genuine attack, for instance, as the result of a cold. Then it is quite a frequent occurrence that both the patient and his relatives lose faith in the treatment, the suggestive power has gone, and the psychogenic attacks recur with renewed force.

There is no doubt that many of the results achieved by doctors and psychologists talking to parents are due to suggestive influence. The same may perhaps be said sometimes of the results of psychoanalysis, but that does not minimise the value of a good result.

Despite thorough examination, treatment of the patient and advice to the parents, it often happens that the home circumstances cannot be improved. It can happen, both from the somatic and psychic points of view, that nothing can be done, no matter how many conversations are held or influences exerted.

In these cases, a change of environment must be brought about, for instance, stay in hospital, convalescent home or other institution, or perhaps in suitable private homes.

Such a stay in other surroundings must be of suitable duration, for example, three months, six months or longer. There is no doubt that such change of environment can, in many cases, save deficient children, including both psychically and somatically deficient children.

An excellent example of the effect of change of environment is the taking of asthma patients from their homes and placing them in new surroundings. We in Denmark send asthmatic children to Refsnæs, Hobro and Norway. Excellent results have been achieved in all these places. Though one should not forget that stays in such places can have a favourable influence on the mucous membranes of the respiratory system, the effect on these children — just as on those admitted to hospital — occurs so quickly that it would seem justified to conclude that much of the beneficial result is due to the change of environment.

It can safely be stated that change of environment is one of the best means at our disposal for treating the more serious psychosomatic disturbances.

I believe that in many cases children can recover so definitely through temporary change of environment that on their return they are better able, at any rate for some time, to withstand their unfavourable conditions.

Conclusion

It will be seen from what I have said that I do not consider psychosomatic disease is any new disease conception. It would be wrong if, in examination and treatment of sick children, more stress was placed on either the psychic or the somatic aspects.

Psychic and somatic factors can separately or jointly cause psychic or somatic disturbances or both.

The central figure in both examination and treatment must be the physician.

Treatment is aimed at improving both the somatic and the psychic condition. The means available consist of somatic treatment, advice to parents, psychic treatment of the child, including suggestive influance and change of environment.

Review of a lecture discussing methods of work in psychosomatic pediatrics

by

GUNVOR VUORISTO, *Finland*

No psychic diagnosis should be made only with the exclusion of organic disease; it must be based on positive psychic findings. On the other hand such findings must not exclude a precise somatic investigation, though, especially with children, unnecessary, painful investigations should be avoided. Both parents and doctors must have as great a respect for the psyche as for bacteria and allergenes.

Weiss and English — in their book "Psychomatic Medicine" — point out that a doctor's ability to take case histories has not kept pace with other advances in medicine. To reveal the psychic connections — often well concealed — demands patience, intuition and good contact with both children and parents. The doctor's personality is just as important as good medical skill. A certain amount of knowledge of psychological and psychoanalytical methods is necessary. More important than the actual facts is often their background.

The diagnostic and therapeutic periods of treatment overlap with no sharply defined boundary. Many releasing factors become clear only in the course of the treatment. Psychical disturbances are usually emotional in character — often an early isolation or an inadequate emotional contact between mother and child, or an insufficient training in cleanliness. Such a conflict is frequently inaccessible through the intellect, so that in later years advice is replaced to a great extent by treatment of both parents and children. In agreement with psychoanalytical principles this treatment should not — especially in the case of older children — be carried out by the same therapeutist.

The nursing staff are trained in the direct observation of children by means of lectures and record sheets. This direct observation is supplemented by various tests adapted to the age and mental development of the child. Different projective tests are used as well as intelligence tests (e. g. Bühler-Hetzer 0—2 years, Cattell 0—2½, Gesell 0—3, Terman-Merrill 2 — adult years, Minnesota pre-school 2—5, Salomaa 4—18, Drever and Collins 5—15, and Goodenough

3—10 years). The results of these must be evaluated against the background of the case histories. Different tests are valuable supplements to each other. For young children their play is the most natural sphere of observation, while little is obtained from them by direct conversation. Besides ordinary games or play the therapeutist can use different, standardised toys both in diagnosis and in therapeutics. At present those said to be most in use in the northern countries are The World Test and Sceno Test. (G. v. Staabs). In investigating the cases of children somewhat older the following have proved useful: — Thematic Apperception Test, Four Picture Test, Szondi and especially Rorschach's method.

Painting and drawing are very suitable for all ages, both in diagnosis and therapy, and have the advantage of being easily accessible for the private practitioner also. In this group too there are standardised methods (e. g. Wartegg test, Koch's Baum test). Graphological tests can be used long before school age is reached.

More and more institutes and advisory centres are making use of different forms of group therapy.

The necessary condition for successful work is intimate co-operation between the psychiatrist, the pediatrist, the psychologist and the social worker.

Asthma as a psychosomatic symptom in children

by

HJALMAR WERGELAND, *Norway*

The fact that asthma is in many instances influenced by the emotional state of the patient has been known for a long time and was recognised by Hippocrates. During the allergic era of the later decades it seems to have been more or less forgotten. In recent years the problem has again emerged due, particularly, to the interest taken in it by the psychiatrists. Numerous investigations have been made attempting to clarify the emotional states of the asthmatic patients, and now there seems to be significant evidence that there is a correlation between the emotional state and the occurrence of asthmatic attacks, in both children and adults. Moreover, the emotional conflict in question seems to be quite specific — in other words, the type of the conflict determines whether the allergic

patient will develop asthma or another allergic condition (urticaria, eczema etc.).

By careful investigation of the emotional state of the asthmatic patients, mostly by means of psychoanalysis, the following trends were found common to all of them: They were overanxious, and very dependent of their mothers or mother substitutes, with a simultaneous wish to remain dependent and to separate from her. The conflict aroused by this ambivalence produced anxiety and fear of loss of the mother's love or of separation from her. This fear would be stimulated by the prospect of actual separation from her — and also by situations where the patient was tempted to do things of which he knew the mother would disapprove. The patient attempted to master this fear by means of a variety of defences, but if he didn't succeed, and asthmatic attack was likely to occur. The breakdown of the defenses mostly occured if the danger of separation from the mother became acute or took the patient by surprise.

The mothers of these patients were found to be predominantly overprotective, mostly as a reaction to a deeply seated hostility towards the child or a complete rejection.

To the objection that these character trends might as well be a result of the disease as the cause of it, it is pointed out that in many cases they could be found prior to the first attack of asthma. On the other hand, the asthmatic disease itself is apt to foster just these character trends in the patients, thereby establishing a vicious cycle.

Many of these patients were relieved of their attacks by psychotherapy alone, regardless their allergic condition. Most pediatricians know about patients who were relieved of their attacks of asthma by hyposensitization or removal of the provoking allergen from the environment, without *other* psychotherapy. This seems to indicate that the psychogenic and the constitutional factors are both responsible for the production of an asthmatic attack, and consequently the therapeutic effort can be directed towards either one of them, or to both of them at the same time. In order to find out which method is likely to bring success, a careful and detailed history, which must consider the psychogenic factors as well as the constitutional, should be taken.

The interaction between the psychogenic and the constitutional forces is theoretically explained as follows: The basic emotional

conflict makes the patients less resistant to the provoking allergens. The resistance can be raised by hyposensitization to a degree sufficient to be free of attacks, and also by eliminating the emotional conflict through psychotherapy. The psychotherapy however has to include the parents, and is best taken care of by an experienced and skilful psychotherapist.

Present Tasks of Psychosomatic Pediatrics

by

SVEND HEINILD, *Denmark*

An analysis of the patients seen during the years 1949 and 1950 in a pediatric out patient department (the Pediatric Reception Unit of the Finsen Institute) in a large city with a view to institution of light treatment or recommendation for admission to a sanatorium for weakly children (Kysthospitalet, Refsnæs) prompts us to set up the following 3 items as the most obvious tasks of psychosomatic pediatrics to-day:

1) *A practical educational work* based on our present knowledge of the normal growth and development of the child. The public is still surprisingly ignorant on this point. Facts are most often misunderstood beyond recognition.

2) *Active participation in social work,* justified by the pediatrician's special qualifications for understanding the importance of social conditions in the development of diseases. Pediatrics must be made "psychosocial".

3) *A scientific work,* for the purpose of elucidating the pathogenic significance of mental as well as physical factors in the development of any morbid process in childhood. A diagnostic system is suggested which has proved serviceable in practice.

From Kronprinsessan Lovisas Barnsjukhus,
Stockholm

Some experience from psychiatric work in a pediatric unit with children suffering from psychosomatic diseases

by

Siv Gunnarson, *Sweden*

Below, some experiences made during the 5-year-period of 1946—1950 at the Department of Child Psychiatry at Kronprinsessan Lovisas barnsjukhus will be related.

At a department of Child psychiatry in a pediatric unit, the majority of cases will show psychosomatic symptoms of various kinds, the somatic symptoms bringing them to a hospital where a negative somatic investigation causes the child to be referred to the psychiatric department.

In the routine work, special attention was paid to the psychological side of sleeping and feeding difficulties, and the hospitalization of the baby.

Close cooperation with the EEG Department of the hospital, with regard to children suffering from convulsions and headaches, provided excellent means for dividing the patients into their respective groups as to the origin of the fits, i. e. whether mainly somatic or psychic. Thus, a better basis for the therapy was obtained.

In the field of psychosomatic disease, scientific investigations were initiated and stimulated by the late Professor Lichtenstein.

In cooperation with the EEG Department (Melin), 90 children with enuresis were examined. The EEG of children who had always been wet since infancy were compared with those of children with dry intervals exceeding one year. Excluding cases with epilepsy, a marked preponderance of pathological EEG was found in the always wet group. The combined results of psychiatric and EEG investigations in these cases strongly support the theory of immaturity in the nervous system as the cause of enuresis in the children, who were always wet. In the group of children, who had a fairly long dry interval, brain changes were less pronounced, and psychological factors seemed to be of major significance.

Together with the Department of Endocrinology (Mossberg) a psychosomatic study was made of children with adipositas. (Refe-

rence may be had to a printed contribution to the discussion.) Among 30 fat children, those showing slight neurotic traits only, with fairly good social and psychic background, all responded well to somatic therapy, losing weight as expected. Among those, showing severe neurotic symptoms combined with unfavourable home conditions, the results of somatic treatment varied. The latter group included all the cases not responding well to therapy. A few had lost weight, but became more maladjusted during that period.

Jointly with the Department of Allergy (Hahn) 60 cases of asthma were studied. (The proceedings of the Ninth Ped. Congress, Copenhagen 1948, p. 68.)

Playtherapy was introduced in November, 1949, on 10 children, suffering from asthma after the attachment of a well trained playtherapist to the staff through grants from the Karolinska institutet.

Our experiments in psychotherapy on asthmatic children may be said to have disclosed several interesting personalitytraits in the asthmatic patients, leading to certain emotional conflicts which, in our opinion, play a great part in the outbreak of asthmatic attacks. However, the therapeutic results, though as yet too fresh to be definitely judged, are most promising.

The first result of playtherapy on asthma in children, counting all our ten cases, is decreasing anxiety during the attacks. The children have their attacks, but take them less seriously. It is as though the anxiety had disappeared. The next step, also passed by our children, is that the nightly throat sound made even when free from attacks, no longer occurred. In some cases, this sound returned in periods of conflict, but disappeared when the conflict was solved. In all the cases, the asthmatic attacks became less frequent than before the therapy. In three cases, concerning children 6 to 8 years old, who all suffered from severe asthma, easily passing into status asthmaticus before the therapy was started, the attacks stopped after 4—7 months of treatment. These three children were subjected to severe colds in the Spring of 1950 without consequent asthmatic sympthoms. This had never happened before. They are still free from attacks or bronchitis. Two children, 5 and 8 years old, earlier suffering from severe asthma, and when the therapy was started still suffering from long attacks of bronchitis, showed severe neurotic traits, causing severe maladjustments at home and in school. Their bronchitis disappeared during therapy. In all 5 children, now recovered, the improvement of the asthma and bron-

chitis was accompanied by a total change in their personality. They are now gay, happy, secure, well-balanced children. This change in their personalities and in view of similar experiences by other authors, render our results very encouraging, suggesting the possibility of a lasting cure of their asthma.

Of the remaining five children, one gave up therapy (resistance on the part of the mother). The other four are still obtaining psychotherapy. However, their asthma has improved, though persisting. The therapy is continued in all the cases.

DISCUSSION

P. PLUM, *Denmark*

There are three points I would like to make:

1. The training of doctors in psychology.

Man is made up both of physical matter and of psyche. Physics and psychology should therefore be the two fundamental subjects in the study of medicine. We learn only a little physics and practically no psychology. What we do learn are the results of experience gained on the basis of the elementary sciences. In order to evaluate biochemical and physical changes it is acknowledged that a certain fundamental training is required in biochemistry and physics. In the same way we must have a certain training in normal and pathological psychology in order to be able to judge the results introduced to us by psychologists.

2. It is essential that, in these problematical fields, we keep in mind a clear picture of what we know and what we do not know. It is also essential that we express this knowledge in a language that is as generally intelligible as possible.

3. There is an immeasurable need in people for psychologic and pedagogic guidance. Pediatricians are in a better position than most to give sound and solid guidance. At the White House Conference on Children and Youth in Washington in December 1950, six thousand pediatricians, psychologists, nurses, social workers, clergymen, lawyers, etc. discussed the subject of "How can we develop in children a healthy personality". It is perhaps natural that we shrink from so great and extensive a task, but we must face the fact of its urgency and of the immeasurable importance of its accomplishment.

C.-E. RÄIHÄ, *Finland*

It has been supposed that the emotional life of premature infants is permanently harmed during treatment in the sterile atmosphere of the oxygen incubator. This would not appear to be the case, as the capillary system which connects the hypothalamus with the anterior lobe of the hypophysis develops late (Niemineva). As no nervous communication exists (Green), the preforming of this vascular system is of particular importance, yet is not generally known. Circulatory insufficiency (as hypotension, prolonged circu-

lation time, anemia etc.), which is unable to fill the system, is significant in deficient humoral regulation.

B. VAHLQUIST, *Sweden*

There is one morbid condition in which the psychosomatic factor is very pronounced, and that is migraine. Particularly in children it is often very apparent that isolated attacks are provoked by mental tension, e. g. going to the cinema, Christmas parties, failure at school, etc., Migraine is more usual in children than many doctors are willing to admit, In an investigation of Stockholm children I found that 2 per cent had had typical attacks before the age of six, and 4—5 per cent before the age of 11—12. In adults the incidence is considerably higher, usually being put at 7 per cent. In treatment of these cases it is essential that consideration be given to the frequently associated neurolabile constitution and to the psychogenic factor of provocation, often distinguishable in the isolated attack. Possible somatic causes must of course also be considered in each case.

Finally a comment on the importance of the much discussed inhibition of aggressions in, for instance, asthma. I should think that it is not always caused by the environment, but is often partially due to a defect in the constitution; in order words, that such children lack the ability to live out their aggressions in the same way as does the average child.

From the child welfare centres in Copenhagen
Chief: Grete Gørtz

Overcrowded Flats as Aethiological Moment of Behavior Diseases in Childhood

by

GRETE GØRTZ, TROELS SMITH, J. RASMUSSEN, I. BOESEN, K. BIERRING-SØRENSEN, P. DRUCKER, E. FOG, A. HENRIQUES, S. HEINILD, H. KREUTZFELD, A. MADSEN, G. ORTMANN, A. SCHONDEL, *Denmark*

About 300—400 cases of overcrowded flats are examined with special reference to behaviour (and infectious) diseases.

As limit for overcrowding a hygienic standard — proposed by the chief medical officer of health of Copenhagen — is used.

This standard, which replaces the older standard of the public-health-act (which claimed 10 m^3 per head), is calculated in this way that a flat is considered to be too little, if there is not present:

1) one room per each two persons.

Besides is claimed

2) that a room must only be occupied by a married couple, persons belonging to the same sex or children below the age of 10 years.

By using this standard, which pays regard to a mental-hygienic point of view, our — up to now rather little — material seems to show that overcrowding is a contributory cause to the origin of behaviour (and infectious) diseases.

A more detailed examination on a greater material will follow in about a year.

Psychosomatic investigations of asthmatic children

by

KNUD WILKEN-JENSEN, NIC WAAL, BODIL FARUP and KJELD BÜLOW, *Denmark*

The problem of the psychologic factors in bronchial asthma in childhood is usually treated in rather vague expressions and in the pediatric literature only little is to be found.

In the out-patient-clinic for children with allergic diseases at the University clinic of Copenhagen (Rigshospitalet) we found at a certain time, that it was possible with the personnel available to submit a number of asthmatic children to a thorough psychosomatic investigation. We started to do so well aware of the difficulties which arose from the performance of all the examinations and tests on each child within the very limited space of 3 days. The children come from all parts of Denmark, and on account of the expenses we are able to keep them in Copenhagen for only 3 days.

Before we saw each patient, an inquiry was sent to his physician regarding the life and conditions of the family and especially the behaviour of the patient.

During the 3 days' visit to the clinic the patient went through a complete physical examination, including a visit to the oto-rhino-laryngologist, had X-rays taken of the lungs and sinuses, was tested with tuberculin and had his eosinophile leucocytes counted. Allergic tests (scratch tests, intracutaneous tests, provocation test) were done by our well trained secretaries or by one of the doctors. A thorough family history starting with the grandparents was taken

by a psychologist, Rorschach test and in some cases Düss-test or T.A.T. by another psychologist, a muscular psychogram was worked out by a psychiatrist and the case history taken by an allergist.

Thus all the patients were seen by 4—5 doctors, 2 psychologists and 2 secretaries, and at staff-conferences all the collected material was discussed and integrated. 45 children over 6 years of age were examined this way but so far a control material has not been obtainable.

The investigations seem to indicate certain characteristic features in the psycho-pathology. The children showed generally affect inhibition, especially suppression of aggression, and — but to a less pronounced degree — sexual conflicts. The material reveals a number of other interesting problems which will be reported at the congress and later published in detail.

DISCUSSION

BODIL FARUP, *Denmark*

The psychological tests have shown fear, inhibition of aggressions, sexual problems, great ambition and repressed productivity, combined with a pronounced mother complex in the majority of children in this series. Many of the children have a rich imagination and live in day-dreams, but cannot translate their dreams into external activity. Others are tied up both intellectually, emotionally and in practically activity. The majority of the group are incapable of exploiting their capabilities satisfactorily, much less optimally. In many there exists a strong desire for opposition which often only expresses itself in roundabout ways.

The series has given rise to the suspicion that the strong mother complex was provoked by certain traits in the mothers, and examples have been seen of opposition when their repressed and improductive asthmatic children became freer and more independent as a result of psychotherapy. Where psychotherapeutic treatment is applied, it should include the mothers.

NIC. WAAL, *Denmark*

Sixty-eight asthmatic children were compared with 55 schoolchildren aged 6 to 15 years with respect to chronic muscular tension and types of respiration.

The asthmatic children were characterized by a special "tension syndrome" not found in the "normal" children: functional constriction of the nasopharynx, lerynx and jaw, and deep throut muscle tension; fixation of the upper half of the thorax, wholly or in part, or impaired movement of the thoracic column during respiration, especially expiration. Seventeen of the asthmatic children showed the whole syndrome the rest several of these symptoms.

Forty-eight patients from the children's asthma clinic were compared with 52 children representing a mixture of various disorders — enuresis, encopresis, other psychosomatic disorders and purely psychopathological conditions. Both

groups were found to have pronounced emotional conflicts, such as repression of emotional expression, inhibition of aggressions, fear, obstinacy, inferiority complex, and sex problems. Statistically, however, there were a greater number of asthmatic children with true repression of emotional expression and inhibition of aggressions; but a lesser number of the emotive, hysterical type than in the other series. The incidence of mother complex was the same in both series, and was high. A dominating mother or father was not found to be characteristic of the asthmatic children. The emotionally inhibited, ambitious type (character neurosis) appeared to be more frequent in the asthma series.

A psychogram of the emotional structure and conflicts of each asthmatic child was made directly on the basis of the tension picture, without knowledge of the results of other examinations and without interviewing the patients. Each psychogram was then compared with the results of Roschach, T.A.T. and Duss tests. There was full agreement between the muscle psychogram and test psychogram in 42 cases, agreement with minor deviations in three, and three were not amenable to testing. There was no failure.

The two series were also compared with respect to environmental factors, a tendency being found which should be investigated further in a larger series. The asthma series showed a higher incidence of parents who were ambitious and emotionally inhibited, or who had suspected emotional conflicts; they demanded obedience and cleanliness at an early age. Most of them came from superficially harmonious homes, in which they took proper pride. In the other series there were more broken homes. The number of children breast fed during the first year of life did not diverge from the average at Copenhagen baby welfare clinics, either in the asthmatic or in the other pathologic series.

With regard to the muscular tension findings in the asthmatic children — the constriction of the upper respiratory passages — infectious processes were found in fifteen. Pathologic changes did not appear to be the reason why all children presented this picture. Since emotional control comes about, as is known, precisely with these tensions, it seems plausible to assume a correlation between these tension patterns and the home environment and emotional inhibitions of the asthmatic children.

All the asthmatic children had emotional conflicts, whether they were allergic or not. The aforementioned factors thus appear to constitute a vicious circle.

Z. ERIKSSON-LIHR, *Finland*

Allergists too are aware that psychic factors play a significant part in the provoking of allergic symptoms, particularly bronchial asthma. We also attempt, wherever possible, to make a psychologic as well as a purely somatic analysis of our patients and to base our treatment on this analysis.

After a careful study of the occurrence of these psychic factors, however, we have come to the conclusion, that they must generally be considered not as primary, but as secondary, having arisen during the course of the illness. I will here merely recall the fact that over 60 per cent of all children with asthma have suffered from chronic eczema for 1—2 years before the onset of the asthmatic symptoms. What this has meant to the psychic balance both of child and mother does not need to be emphasised. Allergists are also

aware that psychologic treatment of the patient should go hand in hand with the purely somatic, and must often continue long after somatic balance has been reached.

The present research on the function of the adrenal cortex hormones is throwing new light on the relation between psychic and purely somatic factors also in allergic disorders, and later in the Congress I shall have en opportunity to give a more detailed account of these investigations.

Both here and in U.S.A. a disturbance of the adrenocortical function, leading in turn to disturbed adaptability to stress, has been demonstrated in at least 70 to 80 per cent of the allergic patients. When the patient is subjected to physical and also, it should be noted, psychic stress, there arises in the place of a restored equilibrium a stage of exhaustion, the typical symptoms of which are a disturbance of the mineral and sugar metabolism, a fall in the blood pressure, hypersensitivity to hypoglycemia, to infections and to histamine — symptoms typical of all allergic diseases, not only of bronchial asthma. These investigations show that behind the so-called psychic disturbances there may be purely somatic disturbances which can be treated with good results.

There is a certain danger in placing too strong an emphasis on the importance of psychic factors in allergic diseases. It can easily make us forget that *an accurate analysis of the purely somatic factors must still form the basis of all treatment of these diseases.*

E. GEDDA, *Sweden*

I wanted to ask the more initiated whether there is not something symbolical in the neurotic behaviour of children, a part of the general symbolism which seems to characterise this field. One is reminded of the symbolism of dreams (terrifying animals as an expression of fear); or the well-known fact that inhibited children play with fences. The same thing might be seen in the circumstance that boys more often practise nail-biting and girls thumb-sucking. One thinks of the only child who gets too much attention and tries refusal of food as a means of escape from at least one form of excessive attention.

The intimate interplay between psychic and physical manifestations is obvious.

B. HAMNE, *Sweden*

In connection with the discussion of migraine in children I would like to emphasize the importance, despite heredity and the clinical symptomatology, of bearing in mind the possible presence of an intracranial tumour.

I recently had a boy of pre-school age with a family history of migraine. For 18 months the lad had had attacks of headache on the left side, ending in vomiting. To start with, the attacks occurred at intervals of a couple of months, but in the last month grew more frequent. Examination revealed papilledema, and it was further discovered that the migraine attacks had commenced during severe pertussis. The patient was operated on at the Neurosurgical Clinic of Serafimer Hospital for a large hygroma over the left hemisphere. It was reasonable to assume that the hygroma had developed from hematoma caused by rupture of a vessel during the pertussis attack.

Upper Respiratory Tract Infections in Childhood from a Psychosomatic Point of View

by

KAREN-ELSE FOGHT-NIELSEN and IB MUNKVAD, *Denmark*

The material consists of a number of children brought to the Finsen Institute, out-patient department of pediatrics, in the year 1950, all suffering from the so-called upper respiratory tract infections.

This group of diseases proved to be a combination of the infection and a number of neurotic symptoms so that the children in reality suffered from a psychosomatic disease.

Many of the infections mentioned above have been classified as streptococcoses and staphylococcoses, manifest as well as latent infections. The diagnoses of the last ones have become clear only by means of special investigations. A great many of the infections have not yet been classified, but are supposed to be caused by viruses.

It has been shown that a number of partly latent neurotic symptoms will be manifest during the stress represented by an infection and it is supposed that a child suffering from a manifest (and perhaps also a latent) neurosis is more easily hit by influences from the surroundings including infections.

On the Testmeal Research and its Psychosomatic Background

by

S. JÄYKKÄ, *Finland*

In the testmeal research the framing of the problems has generally concentrated on the estimation of the so-called normal acid values with children. Against the earlier opinion Kurt Kaijser proved that the HCL, Cl, and pepsin concentration in the gastric juice of a child is chiefly the same in children from new-born infants up to the age of fifteen years.

It is a generally acknowledged fact that the emotional state has a great influence on the stomach secretion. The purpose of this

investigation is to ascertain whether there are — and how frequently — achlorhydria cases that can be ascribed to the emotional state, if we use the routine Boas-Ewald testmeal.

Eighteen children of the age of 2—4 years were examined. Among them 8 cases of functional achlorhydria were found which could be explained as due to an emotional state of fear (alarm reaction involving fear). If the child was in such an emotional state, the HCL values generally were lower than when the child was calm. By using Histamine it is possible to cause a secretion, although the child is in an emotional state of fear, but even then values remain low.

The achlorhydria result has been considered of etiological importance in the estimation of the chronic stomach troubles with children. As we, however, do not know any pathological anatomical equivalent, and taking into account the psychic factors, one must use caution in the consideration of an achlorhydria with the testmeal in children. The same can be said of the usual substitute therapy for achlorhydria, the HCL-drops, which are mere likely psychotherapy than substitute therapy.

From the pediatric department of Copenhagen County Hospital in Gentofte. Chief: P. W. Brœstrup, M.D.

The treatment of psycho-somatic disorders in childhood with special reference to treatment primarily of the mothers

by

P. W. Brœstrup and G. Ricklefs

The increasing number of children with psycho-somatic disorders during later years made it impossible — within the capacity of the ward — to treat them all with play-therapy. Therefore, we have tried, on a purely experimental basis, to take a shortcut by treating the environment of the child, in suitable cases.

Since april 1950 all children with somatic complaints who have a possible psychological background for their complaints, have after a thorough medical examination, been referred to the psychologist (G.R.).

The psychological exploration consists of:

1) examination of the child with intelligence tests, Rorschach, TAT and other projective technics as well as observation in the sand-box.

2) Interviews with the parents or other persons in close contact with the child.

At the same time the daily behaviour of the child is observed by the medical and the nursing staff and the kindergarten-teacher. In a joint conference it is then decided what kind of guidance and/or therapy should be given to the patient and/or the mother.

In some few cases the child has been treated with play-therapy. In the majority of the cases the treatment consists in guidance or "therapy of the home", further interviews with the mothers, alone or in groups of mothers with similar problems.

In group treatment of mothers the psychological development of the child, its deviations and their causes are discussed. The group consists of 6—8 mothers and each group is given 6—8 hours of discussion.

The capacity of a full-time psychologist has for the first 11 months been as follows:

Total 167 cases.

110 cases given the standard examination outlined above.

28 — with group-treatment of mothers.

12 — with more prolonged treatment of either child or parents.

17 — intelligence testing only.

This also includes 23 children with simple behaviour disorders, examined to determine future therapy and placement.

The following results have been obtained in the cases of enuresis:

Total 52 cases.

18 with group-treatment of mothers.

32 with the standard examination only.

2 with play-therapy.

The results of the treatment are as follows:

22 children have been completely free of bedwetting over a period of more than 3 months.

14 children: the mothers report considerable improvements.

5 are reported to be as before the treatment.

8 just dismissed.

3 without any report.

An effort has been made to limit the routine admission time to

21 days, and 10—12 days would seem even more desirable. During this first year, well over one third of the cases have been dismissed in less than 20 days and more than 50 % in 25 days or less, but there is still a relatively great number of children who have been kept longer in the wards, waiting for a room in a convalescent home etc. Considerable shortening of the admission time in these cases can be foreseen.

On Psychogenic Obesity in Children[1]

by

TORBEN IVERSEN, NIELS JUEL-NIELSEN, FLEMMING QUAADE, KAI TOLSTRUP and LISE ØSTERGAARD, *Denmark*

This report is a summary of five answers to a prize question in clinical medicine on Hilde Bruchs' theory on psychogenic obesity in childhood, set by the University of Copenhagen in 1949.

Bruch's investigations were published in Am. J. Dis. Child. *59*: 739, 1940, Psychosom. Med. *2*: 141, 1940, Am. J. Orthopsychiat. *11*: 467, 1941, and Am. J. Psychiat. *99*: 752, 1943.

Iversen studied 40 children, 15 boys and 25 girls, 4—14 years of age, who had been admitted for simple obesity to the Pediatric Department, University Clinic at Rigshospitalet, Copenhagen, and to the Dronning Louise's Children's Hospital, Copenhagen.

Psychologic factors might be supposed to be of genetic importance in 16 cases, while such factors were questionable and uncertain in 14 cases and absent in the remaining 10 cases. A non-rejecting maternal overprotection was disclosed in 20 cases. In 4 cases, all boys, the constellation was similar to that described by Bruch.

Juel-Nielsen reexamined 61 obese children, 25 boys and 36 girls, 2—14 years of age, admitted to the Pediatric Department, University Clinic at the Aarhus Municipal Hospital and to the Medical Department at the Aarhus County Hospital.

It was not possible to record the special social-psychologic structure, which in Bruch's opinion is characteristic of obese children's surroundings. The author was able to point out a certain psychogenic etiology of rather varying type in 9 cases, 3 of which had an

[1] To be published in Acta Pædiatrica.

apparently classic Bruch-character. In 12 cases the psychogenic etiology was uncertain, and in 40 cases is was negative.

Quaade selected a material representative of the obese children who attended four Copenhagen County Council Schools. The group comprised 36 obese children, 18 boys and 18 girls, 6—16 years of age.

It was concluded that Bruch's theory is too specific to explain the etiology of obesity in childhood. The author is of opinion that the great majority of obesity cases have their origin in and are maintained by non-pathologic eating habits that probably involve problems of geographic, religious, and ethnologic nature, as well as principles of food hygiene.

Tolstrup examined 40 obese children, 14 boys and 26 girls, one being 1 year, the rest 7—16 years of age. 22 children were selected from the school physicians' card-index as the most obese out of 5 000 school children in the city of Odense. 18 children had been admitted to the Odense County and City Hospital.

From an etiologic point of view the material could be subdivided into three groups: A. 7 cases with positive psychogenesis; 3 of these were of the type described by Bruch. B. 11 cases with probable psychogenesis. C. 22 cases where no psychogenesis could be established. As a whole, no characteristic family frame was demonstrated.

Østergaard made psychologic investigations in 58 children, 20 boys and 38 girls, 5—14 years of age, who had been treated for obesity at the Dronning Louise's Children's Hospital, Copenhagen.

43 children had difficulties in making contacts with other children. 49 children were Rorschach-tested; a very large part showed symptoms of insufficient emotional adjustment, infantile affectivity and neurosis. The intelligence quotients showed a normal distribution. 49 cases could be classified as psychogenic obesity, among which the typical Bruch-constellation was noticed in 14 cases.

A total of 235 children, 92 boys and 143 girls, have been studied to disclose possible psychogenetic factors in obesity.

As the authors have worked separately and with heterogeneous materials, a direct comparison of the results is not possible. Nevertheless, it may be concluded that psychologic factors explain many obesity cases in childhood, even if the psychogenesis is not so specific as described by Bruch.

Eating problems in children

by

Sven Frandsen and Per Jacoby, *Denmark*

Certain aspects of the eating problems in children have been investigated. The series of cases comprises the children, a total of 1575, referred in 1950 to the Pediatric Reception Unit, the Finsen Institute. Of these, 403 had "an eating problem", by which we understand that the question of food intake differs essentially from the normal view and treatment of this process in the child. It is pointed out that we have not included cases of shorter or longer loss of appetite in a child, where this has been looked upon and treated in a tolerably sensible way.

The ages of the 403 children, or 26 % of those referred, ranged from 6 months to 13 years. The majority were from 2 to 7 years. 230 were boys and 173 girls. In 96, or 24 %, the eating problem was the only or the main cause of the reference. The remaining 307, or 76 %, had been referred for other reasons, and the eating problem was here disclosed by questioning the accompanying person. The patients represent the "weakly children" of our times, all referred for light treatment or recommendation for admission to a sanatorium. The eating problem is, of course, particularly great among these. The incidence in a more representative series of Copenhagen infants, as is available in an Infant Control Station, has been found to constitute 11 % out of 819 infants between the ages of 15 months and 6 years.

By questioning the person accompanying each child, and examining the child itself, we have managed to elucidate various factors of importance for the development and explanation of the eating problem. The investigations showed that — at least in this country — numerous parents and others taking care of children have absolutely wrong, even grotesque ideas of the simplest physiological and emotional facts relating to children's eating. This applies particularly to constitutionally asthenic, or better leptosomatic children, whose special type, differing from the average, is rarely acknowledged. In numerous homes the eating problem of the children, specially of this type, has become unreasonably great and for years given rise to perpetual conflicts and unnecessary concern.

DISCUSSION

SIV GUNNARSON and HANS-OLOF MOSSBERG, *Sweden*

Since the spring of 1950 an investigation has been proceeding into the psychic conditions of adipose children at the Crown Princess Lovisa's Children's Hospital. The patients had been submitted to thorough somatic examinations by Mossberg at the outpatient department of endocrinology, then given somatic treatment and subjected to frequent follow-up examinations for one to four years. Some had responded well to the treatment and lost weight as expected, but others had shown little or no loss of weight. Several from the first-named group had relapses. Thirty patients from Mossberg's series were submitted to psychic examinations. A social worker trained in child psychology investigated the environment; mothers and children were seen by the child psychiatrist; and intelligence and Rorschach tests were carried out in each case.

All save two were stated to be sensitive children who had early found difficulty in meeting the everyday trials of life, such as quarrels with playmates, etc. In most cases the sensitiveness was manifested long before the adiposity became a psychic trauma. Two-thirds of the mothers were overprotective toward the children, keeping the children dependent on them and bound to them much longer than is normal. In all thirty cases the Rorschach test showed neurotic symptoms of varying degree. In one half of the cases the children's environment was conspicuously bad. A certain correlation between weight gain and psychic factors was found in 24 of the 30 cases; e. g., a rise in weight on starting school, associated with anxiety at the thought of a strict teacher or the like.

The children with only mild neurotic symptoms whose environment had been satisfactory had all responded well to somatic treatment of the adiposity; the poor results of this treatment were all assignable to children with severer neurotic symptoms and bad environments. Some of them had lost weight under treatment but had rapidly increased again when the latter was discontinued. In some cases the neurotic children had reacted with acute nervous symptoms and impaired adaptation during periods of strict dieting. Factors which in particular seemed to impair the results of somatic treatment consisted in bad environment, especially when the mother alone was in charge of the child or was overprotective.

Einige Gesichtspunkte zum Enuresisproblem bei Volksschulkindern

von

SIRKKA-LIISA HELMINEN, *Finland*

Die unter den Volksschulkindern (7 025 Kinder) der Stadt Turku (Åbo) gefundenen 220 Bettnässer wurden unter besonderer Beachtung der physikalischen Pathologie, Intelligenz, Heredität und sozialen Verhältnisse untersucht. Unter den Hilfsschulkindern

ist die Zahl der Enuretiker auffallend höher (120 Kinder—10 Enuretiker). In manchen Fällen ist die erbliche Disposition nachzuweisen; die schlechten sozialen Verhältnisse bei neuropatisch veranlagten Kindern scheinen oft die Veranlassung zur Enuresis abzugeben. Eine auf das Kind und die Angehörigen zugeschnittene Suggestionsbehandlung wird mit gutem Erfolg angewandt.

On factors influencing the menarche age in Finland

by

G. A. Simell, *Finland*

The material has been compiled chiefly in person, a part also through teachers of gymnastics and school-nurses. The material has been gathered from all over Finland. 5 741 cases comprise persons born in the year 1923 and thereafter.

For the investigation of mental achievements, the average values of the subjects of instruction in the school-certificates have been counted.

The average menarche age in Finland is	14.24 years
That of independent mental workers	14.03 years
That of employed mental workers	14.13 years
That of independent physical labourers	14.39 years
That of employed physical labourers	14.33 years
That of the Swedish speaking in Finland	13.89 years, and
of the Finnish speaking	14.26 years

The weighted figure for the menarche age in Finland is 14.32 years: 14.36 years in respect of Finnish speaking and 13.91 in respect of Swedish speaking. These figures have been checked and the differences are statistically significant.

The menarche shows an uneven distribution with respect to the months of the year. June, with 12.7 per cent, has the highest proportion, bein followed by January, September and December. The menarche coincides with the month of birth in a very high proportion — 11.9 per cent. The figures and differences are statistically significant.

Menarche and attending mental reactions

by

KIRSTEN AUKEN, *Denmark*

As part of an investigation into the sexual development of young females 314 women between the ages of 20 and 36, admitted to 6 different hospitals about in Denmark, have been asked when menstruation first occurred, and if they knew anything about it before its occurrence.

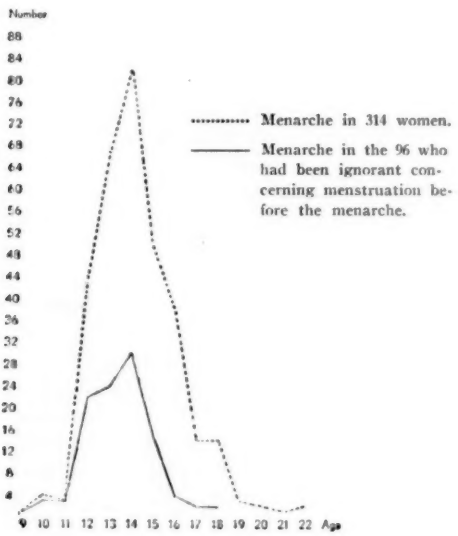
The average age for all 314 was 14.2 years.

96 (30.6 %) had been ignorant about menses before the menarche.

Of the 42 women aged 12 at the menarche 21 had been ignorant about menses (50 %).

Of the 85 women aged 14 at the menarche 29 had been ignorant about menses (34.1 %).

Of the 49 women aged 16 at the menarche 3 had been ignorant about menses (6.1 %).



Out of 122 women with childhood in the country 33 (21.0 %) had been ignorant about menses at the menarche.

Out of 165 women with childhood in a town or city 56 (33.9 %) had been ignorant about menses at the menarche.

Of the 96 with no knowledge of menstruation at the menarche 21 had been "surprised", but had felt no fear.

75 had reacted very strongly. Of these, 15 had believed that they were severely ill, while 46 stated that they had felt a pronounced fear, in 7 of a rather violent character. 8 had thought they were going to die.

The average age for the menarche was 13.4 years for these 75 women, of whom 21 were under 13. 10 of the 75 concealed the occurrence of menstruation from their associates for a shorter or longer period, up to 6 months.

DISCUSSION

TORBEN IVERSEN, *Denmark*

None of the patients in the collected series has shown signs of endocrine disturbances. The patients in the hospital series received a routine examination in this respect (basal metabolism, 17-ketosteroids, serum cholesterol, etc.). The patients in the school series were examined if any endocrine disorder was suspected.

From the E.E.G.-laboratory, Dronning Louises Børnehospital, Copenhagen

Electroencephalographic Findings in Patients with Cerebral Palsy (Little's Disease)

by

HELGA and SVEN BRANDT, *Denmark*

Through pneumoencephalography information about anatomical defects and their localisation can be obtained. Electroencephalography (E.E.G.) may demonstrate abnormal activity of cells in the brain. In addition to the clinical-neurological examination these two methods are able to give us a more complete picture of the extent of the disease.

Up to April 1951 2 adults and 45 children with cerebral palsy (4 months to 15 years of age) have been examined at the E.E.G.-laboratory at Dronning Louises Børnehospital.

Among 19 patients who had epilepsy or who had previously shown epileptic manifestations electroencephalographic abnormalities were found in 16. In 12 of these 16 patients there were focal changes though only 5 had convulsions of focal nature.

27 patients had never had epileptic symptoms but in spite of that abnormal E.E.G:s were found in 17, chiefly non focal changes (too slow a dominant frequency for the age; too many high amplitude slow waves; too rapid a dominant frequency), as indicating of a diffuse cortical dysfunction or functional changes of subcortical origin. In 7 there were only focal changes (spike and waves or high amplitude slow waves).

Among the 47 patients there were 14 with spastic hemiplegia. An abnormal E.E.G. was found in 12, mostly with focal changes in the opposite hemisphere either in the motor cortex or in silent regions. In 3 there were also changes of focal character in the homolateral hemisphere.

Focal changes were found most often in E.E.G:s from patients with asymmetric types of cerebral palsy (hemiplegia, quadriplegia). In children with diplegia or paraplegia the E.E.G:s were either normal or they showed a diffuse dysrythmia.

DISCUSSION

KARL-AXEL MELIN, *Sweden*

With their investigations Helga and Sven Brandt have shown us that electroencephalography may take us another step further in our attempts to elucidate the conditions affecting spastic children. I have nothing to add in the way of facts; for their experience is quite consistent with that we have gained at the Kronprinsessan Lovisa's Children's Hospital. The focal findings are common in our series too.

However, I would like to take this opportunity of calling for better care of spastic children. In Sweden, as in the other Scandinavian countries, we are very backward in this respect; if indeed any care of spastic children occurs at all. The embryo of an organization for this purpose has come into being here and there, but for preschool children in particular there is very little possibility of having their skills developed and trained in a satisfactory manner. Our researches are continually providing us with new methods of examination and treatment, which must be tested further and come into more general use if they are found to be really effectual. But as things are today, we lack in great part the proper facilities. A body of opinion, led and supported

by pediatricians, should call for action on this matter. We are here concerned with several hundred children of normal or almost normal ability in each of the Scandinavian countries who could be made fully or partially capable of supporting themselves; whereas at present they either constitute a heavy burden to their families or are inmates of institutions which give them the proper care but do nothing to develop their potentialities.

In Sweden there have been a few inquiries, instituted by those responsible for the care of cripples and the disabled, into the position of spastic children, and they have led to the planning of a school-home accommodating sixty children. Yet it has been almost entirely overlooked that there are also spastic children of preschool age, and that the care of these is perhaps the most important of all. A group of pediatricians, child psychiatrists, psychologists, educationalists, etc., on the Swedish Committee of the Organisation Mondiale pour l'Education Préscolaire are at present urging the authorities to sponsor an experimental scheme embracing an institution for small children, accommodating twenty inmates, and in conjunction therewith a kindergarten for less severe cases where the parents' or guardians' share of the necessary care and treatment could be supervised. Although this plan has gained a hearing to some extent, its realization will require strong support, especially from pediatricians.

R. AMLIE, *Norway*

At the Children's Clinic of the National Hospital in Oslo we too now have a small department for cerebral paresis. And we have there used electroencephalography in the routine examination of patients, Dr. G. F. Henriksen having undertaken the readings for us. As yet the series is too small for us to present any statistical analyses. We can detect, however, a somewhat different distribution than the one found by Dr. Brandt.

A large number of our electroencephalograms are described as being within the limits of variation permissible for the age. Some of them show dysrhythmia, but we have found considerable dysrhythmia in minor brain lesions and only slight dysrhythmia in major ones.

For us the examination has been most valuable in those cases in which we have been able to find epileptogenic disorders which could be treated. We found in our series a much lower percentage of epilepsy cases than did Dr. Brandt in his; but this was doubtless because ours was selected due to the shortage of beds.

L. SALOMONSEN, *Norway*

In conection with Dr. Melin's statement that the treatment of spastic children has been neglected in Scandinavia, I would like to point out that exceedingly good results can also be obtained with very modest means. At the Children's Clinic in Oslo we have instituted systematic treatment of these patients solely with the help of a specially trained kinesitherapist. Yet, despite the fact that we have lacked those other members of the team who are necessary for really effective treatment, we have nevertheless obtained very good results with means that are simple enough to be carried out readily at any children's hospital.

SVEN BRANDT, *Denmark*

During the past four years a few children with severe cerebral palsy have been treated in the Department of Pediatry, Rigshospitalet. A specially interested nurse was assigned to establish close and frequent contact with the children, and in those with impaired speech to carry out simple but fundamental exercises of the speech organs. The patients were also treated by therapists from the Department of Physiotherapy of the hospital.

In the past year The Association and Home for Cripples have also initiated more thorough investigation of children with cerebral palsy at the school of the institution. The patients were examined by a team of neuropediatrician, physiotherapist and orthopedist, who thereafter discussed the possibility of improving the treatment of each individual child.

Finally, the above Association has appointed a committee to inquire into and submit a report on the problems of these children. On the working subcommittee of six, Danish pediatrics have two representatives. The primary aim is to improve the facilities for treatment of the youngest children, and for this purpose to seek to establish a therapeutic school and home for children between the ages of two and seven years.

Capillarymicroscopic examinations of the conjunctiva capillaries of premature infants and their sensitiveness to adrenaline

by

TERTTU ARAJÄRVI, *Finland*

Bloodvessels of the conjunctivas of fullterm and premature newborn infants were examined using a binocular capillarymicroscope, Reichert's make, magnifying 20 and 60 times. The source of light was a lamp moving with the microscope. The light was directed obliquely at the eyeball. Thus the bloodvessels of the conjunctiva were clearly seen against the light background. The eyelids of the child were drawn aside by means of a lidretractor.

The examinations prove that the meshes of the capillary network of a newborn infant are dispersed in disorder. In some parts of the conjunctiva they are more dense and in other parts more scattered. Gradually the network becomes more regular, in fullterm infants at the age of 3—6 weeks and in premature infants at the age of 4—8 weeks. Early the prematures have less capillaries than the fullterm infants.

Also the sensitiveness of capillaries to adrenaline was examined. The capillaries were stimulated locally by dropping adrenaline solutions, of various strengths, on the conjunctiva and by giving different amounts of adrenaline by injection. At the present, it appears that in those whose birthweight is about 2 000 grs or less, a 1 : 100 000 dilution of adrenaline needed locally to effect a contraction of capillaries (fullterm infants 1 : 1 million) and by injection, 0.01 mg adrenaline (fullterms 0.005 mg). The periods of this defect in action vary depending on the development of the premature in question. If the development is normal, the defect passes in 1—2 weeks.

DISCUSSION

ESTER SELESTE, *Finland*

In connection with Dr. Arajärvi's paper, I would like to ask two questions.

Since the erythrocytes are known to form agglomerations in infectious conditions and in erythroblastosis, it would be interesting to know

1. If, Dr. Arajärvi's method will show whether or not the newborn has an infection and if so,

2. whether it is possible by means of these examinations to verify a diagnosis of erythroblastosis and perhaps to judge the degree of severity.

T. ARAJÄRVI, *Finland*

In infectious conditions one can distinctly see erythrocyte aggregations, the size of which increases with the degree of severity of the infection. One can also observe a decrease in their size as the infection abates.

In this connection I would mention that the customary instillation of silver nitrate solution into the eyes of the newborn disturbed my examinations in so far as it produced mild inflammation besides small aggregations of erythrocytes. For this reason the instillation was discontinued while the capillaries were being photographed.

As is evident from the photographs which Dr. Broman is exhibiting here, very large aggregations of erythrocytes are present in the blood of infants with erythro blastosis, and disappear in the course of blood transfusion. I have observed the same thing with the capillary microscope, as well as a tendency for the aggregations to be larger in more severe forms of erythroblastosis.

Physiological aspects of the oxygen treatment of premature infants

by

Erik Malm, *Finland*

In order to estimate the degree of respiratory insufficiency, the oxygen consumption of premature infants of different birthweights was determined during the first weeks of life by means of an open circuit system, the details of which will be published later. In the smaller weight classes, there is an increase in the oxygen consumption when the infants breathe oxygen-nitrogen mixtures containing 40—60 per cent oxygen. This increase is less commonly observed and smaller in the higher weight classes of premature infants, and does not occur in healthy full term babies.

The oxygen saturation of the blood of prematures increases when the oxygen content of the inhaled air is raised. However, there was no statistical difference between the blood oxygen saturation graphs of premature infants, treated at the hospital, in air or in an incubator, where a 40—60 per cent oxygen mixture was used.

A comparison of the volume of trachea-main bronchi and the volume of the lungs in foetuses and prematures weighing from 60 to 3 000 grams indicates, that the smaller a foetus or a premature infant the higher the ratio trachea-main bronchi: lungs.

DISCUSSION

A. YLPPÖ, *Finland*

Dr. Malm's interesting investigations, which show that an increased supply of oxygen is not bound to produce a rise in the oxygen content of the blood, cannot be interpreted to mean that the oxygen treatment of these premature infants would be of no value. For maximal oxidation of the blood in prematures is dependent on the special character of the blood, and this such that the hemoglobin cannot take up more oxygen. The fact is, however, that if the supply of oxygen is increased, more oxygen will be consumed.

On Asphyxial Membranes in Lungs of Newborns

by

E. K. AHVENAINEN, *Finland*

Asphyxial membranes are seen alone or combined with other diseases of the lungs or other organs. Fairly often asphyxial membranes are the only finding at the autopsy of a newborn infant. The symptoms of asphyxial membranes are reviewed on the basis of such cases. Most of these babies died during 24 hours after birth. The pregnancy was seldom regular. The delivery was often rapid. The babies became severely cyanotic and dyspnoic in a few hours after birth and these symptoms lasted — temporarily relieved by oxygen — until death. In the differential diagnosis congenital heart failure, congenital pneumonia, and brain injury are to be kept in mind. Often the clinical diagnosis of asphyxial membranes can be only assumed.

The genesis of asphyxial membranes is discussed. The theory is presented that asphyxial membranes develope as a result of aspiration of swallowed and vomited amniotic fluid. Animal experiments supporting this view are presented.

DISCUSSION

A. YLPPÖ, *Finland*

Previously we have thought that these so-called asphyxiant membranes develop chiefly during intrauterine life. Ahvenainen's investigations suggest, however, that postnatal vomiting and aspirations perhaps play an even more important role. This explains why asphyxia often does not occur until several hours or several days after birth.

S. RANSTRÖM, *Sweden*

The fact that no correlation is found between the content of vernix caseosa particles and the amount of hyaline membranes in the lungs suggests that aspiration of amniotic fluid does not play any essential role in the membrane formation. As Dr. Ahvenainen pointed out, the greatest importance assuredly attaches rather to aspiration of the gastric contents. The membrane formation is due to the deleterious effect of the gastric juice on the bronchial-alveolar epithelium, together with exudation of protein material (*cf.* the formation of identical hyaline membranes in adults with influenza, lesions due to war gases, etc.). Atelectasis must be considered a major cause of death in these case; for it is the chief morphologic change, even though the membranes are perhaps the most conspicuous.

L. SALOMONSEN, *Norway*

Salomonsen asked the Finnish representatives whether they considered bronchoscopic aspiration to be therapeutically indicated in cases where asphyxiant membranes were suspected.

Y. ÅKERRÉN, *Sweden*

Åkerrén described a few cases of asphyxia in newborn infants with pulmonary atelectasis, in which laryngoscopy and aspiration of bronchial contents led to an improvement and resulted in recovery. One case with the diagnosis of asphyxiant membranes, later verified at autopsy, was treated in the same way without success. It seems in the nature of things that asphyxiant membranes will not be amenable to laryngoscopy and aspiration. — Åkerrén stressed the importance of gastro-intestinal administration of oxygen in measures in the respiratory tracts of asphyctic newborn infants.

E. MALM, *Finland*

In connection with Professor Salomonsen's question I would like to point that at the Children's Clinic in Helsingfors we have not yet had any experience of bronchoscopy and aspiration of bronchial contents in asphyctic infants. In a few cases, however, we have administered oxygen under a pressure of 6—10 cm water with the aid of a small rubber mask. Following this we have been able to observe an improvement in the condition and have not seen any deleterious effects. Nor have there been any signs of ruptures in the lungs of those infants who have died.

JOHN LIND and C. WEGELIUS, *Sweden*

In the discussion on asphyxia in newborn and premature infants, reference should perhaps be made to the cardiac considerations. During the first few days of life the postnatal adjustment of the circulation has a functional basis and is therefore reversible. The development of the right heart is commensurate with that of the left, and this facilitates a reversion to fetal conditions. If, for instance, there should appear during the first few days of life an atelectasis or some other pulmonary complication that increases the pressure in the pulmonary circulation, the requisites will be present for a reversed, *i. e.* fetal, direction of flow in a ductus arteriosus that is open. We have been able to observe this at Nortull Hospital in angiocardiographic examinations of infants with persisting cyanosis, or attacks of the same, during the first few days of life. We have also seen cases representing the other postulated condition for a fetal direction of flow; namely, an open foramen ovale with a shunt from the right to the left auricle, which condition must lead to cyanosis or increase it if already present.

PER SELANDER, *Sweden*

Dr. Ahvenainen has of course shown that the aspiration of various fluids may give rise to membranes in the alveoli. I would merely point out that the question of the membranes due to aspiration that are seen in newborn

infants is debatable. Miller and his coworkers have taken up this problem again, and their series has brought to light some interesting points. For instance, the hyaline membranes were rarely found in stillborn infants and in infants of mothers where parturition had been complicated. And it is just in these groups that aspiration should be especially common. The membranes occurred in prematures. Indeed, Miller and his associates consider this so typical that if a healthy woman in normal labor gives birth to a premature child which dies within 48 hours, the presence of hyaline membranes can be predicted with the greatest probability. Hence they are inclined to regard it as a question of damage to the epithelium in the alveoli and bronchioles.

On the basis of these observations Provenzano and his coworkers have tried the administration of extract of the adrenal Cortex in such cases, and claim to have obtained an appreciable improvement in the respiratory distress.

From the Surgical Department, Children's Hospital, Gothenburg, Sweden. Chief: G. Pettersson

Brachyoesophagus and Insufficiency of Cardia in Children

by

GUSTAF PETTERSSON, M.D. *Sweden*

During the last two years, 8 patients with cardial insufficiency have been treated at the Surgical Department, Children's Hospital, Gothenburg. Every case was verified by X-ray examinations of the oesophagus with the patient in Trendelenburg's position. In case of cardial insufficiency, the contrast material is refluxed into the oesophagus. Three of the patients were less than 6 months old, four between 6 months and 2 years, and one was 7 years old. In five cases, the symptoms had been observed from birth up, in three cases the first symptoms were observed from 1—8 months after birth. All patients had vomited daily, and three of them occasionally had vomited blood. X-ray examinations showed cardial stenosis in three cases; one case had a positive picture and another case a suspect picture of oesophageal peptic ulcer. After X-ray examination and thoracotomy, the material can be grouped according to the pathological findings:

Group A.: 6 cases with brachyoesophagus and partial displacement of the stomach above the diaphragm.

Group B.: 2 cases with a wide cardial opening and, consequently, a wide oesophageal hiatus.

Crushing of the left phrenic nerve was performed in 5 cases in group A, after which 2 cases were completely and one case almost free from symptoms. In three cases, thoracotomy and fixation of the diaphragm above the cardia, had to be done. Postoperatively all showed cardial sufficiency and were almost free from symptoms.

In one case of group B, crushing of the phrenic nerve was tried unsuccesfully. Afterwards, thoracotomy with surgical narrowing of the oesophageal hiatus was performed. Postoperatively this patient had cardial sufficiency and was completely free from symptoms. The other case in group B was operated upon with the same method and the same gratifying results.

The author wants to stress the importance of early diagnosis so that adequate treatment can be given, before oesophageal peptic ulcers and stenosis have developed.

On the blood minerals in pyloric stenosis patients

by

Jyrki Kauhtio, *Finland*

In the Children's Clinic of Helsinki, sodium and potassium determinations (by means of a flame photometer) have been performed on the plasma and the erythrocytes of surgically treated pyloric stenosis patients. The material consists of fifteen cases all of whom have recovered. The plasma potassium at the beginning of the treatment was in all cases decreased, even to values below three mEq./l. and returned to normal during the treatment. The plasma sodium values were low in some cases, but some supernormal values have been found. The changes in the red cells were similar in all patients: At the beginning of the treatment the erythrocyte potassium was distinctly decreased, the mean value being 82 mEq./l., and the sodium correspondingly increased the mean being 32 mEq./l. During the treatment the values returned to normal; potassium 97 mEq./l., sodium 18 mEq./l.

The electrolyte concentration of the erythrocytes as such can scarcely be held to represent the situation in the whole organism. However, the low potassium content of both the plasma and the red cells seems to indicate a potassium deficiency of the organism. The

dehydration and poor food intake found in these patients would easily explain the occurrence of such a deficiency. As a consequence, the use of potassium containing saline solutions in the preoperative fluid treatment would seem rational.

DISCUSSION

P. W. BRÆSTRUP, *Denmark*

Bræstrup requested further information on the following points:

1) What treatment (administration of potassium) was used in those cases in which the potassium values were normalized parallel with normalization of the serum bicabonate.

2) What conditions were laid down with regard to normalization of the blood electrolytes *prior to* operation.

Y. ÅKERRÉN, *Sweden*

Åkerrén asked whether Ringer's solution is a satisfactory form of potassium administration in pyloristenosis with hypopotassemia. Blood transfusion should be a rational form of administering potassium. — Calling attention to the abnormal electrocardiograms demonstrated in pyloristenosis, he asked whether they might have any connection with hypopotassemia, if present.

P. SELANDER, *Sweden*

If we have to deal with pyloric stenosis and lack the facilities for electrolyte studies, electrocardiography will be of considerable help. Abnormal electrocardiograms had been found in pyloric stenosis even before Darrow demonstrated a disturbance of the potassium balance in diseases associated with diarrhea and vomiting. The Q—T time is found to be prolonged, and the T wave often double. The electrocardiogram resembles that most frequently found in hypopotassemia. It is normalized parallel with hydration (with Ringer's solution). This is most certainly due to disturbances in the electrolyte balance and the acid-base equilibrium. Although abnormal electrocardiograms do not seem to be a constant finding, the electrocardiographic examination is of good service. Potassium deficiency may of course occur even if the serum potassium is normal.

J. KAUHTIO, *Finland*

Although our investigations are not yet complete, we have the impression that administration of sodium chloride solution in potassium deficiency makes the physiologic rehydration difficult and combats the infiltration of sodium into the potassium-deficient erythrocytes. If in addition to sodium a sufficient amount of potassium is available, the erythrocytes appear to be selective and the retention of sodium will be considerably less.

Rehydration should preferably proceed continuously between the extracellular and intracellular phases. If one administers Ringer's solution, in

which the potassium content is low, or sodium chloride solution alone, the low plasma potassium level will fall further and we may observe *e. g.* typical electrocardiographic changes, which we too have been able to find in diarrhea cases with potassium deficiency.

In the present series we administered Darrow's solution, approx. 50 cc per kilo per day, until the amount of food after operation had risen to at least 400 gm per day. This quantity, however, appears to be insufficient.

The patients in this series were operated upon, regardless of mineral determinations in the erythrocytes, as soon as the alkalosis had decreased, usually after two to four days.

On the use of intravenous fat emulsions

by

VILJO HALONEN, *Finland*

The author used an emulsion of olive oil with fresh egg lecithin as stabilizer. The latter does not produce histological changes in experimental animals, as does the soy bean lecithin used by most other authors. In tests on rabbits the emulsion was found to be pyrogenfree and it may be preserved, sterilized, for at least 6 months. The emulsion was administered intravenously to some infants. The only untoward effect was a transient hemoglobin decrease of about 10 %.

From the Children's Clinic of the University of Helsinki
Head: Prof. Arvo Ylppö, M.D

Alimentary Chylomicronæmia in Children

by

P. ERMALA, *Finland*

The main part of the alimentary fat, absorbed through the lymphatics is present in the blood postprandially as small particles called chylomicrons. With the ultramicroscope their number and its variations can be estimated similarly to that of the other particulate elements of the blood. For the study of fat metabolism the chylomicron method is, as compared with chemical methods, simpler, especially for the pediatric purposes. A quantitative method for

the determination of chylomicronæmia as well as a clinical fat-tolerance test have been modified by the author; a micromethod, which requires only a drop of blood and the study of one sample takes only 5 to 10 minutes.

In the present investigation the main attention was paid to the physiology of the chylomicron metabolism in children. Alimentary chylomicronæmia depends upon the quality and the amount of fat administered. The individual as well as the interindividual variations after a moderate fat meal, however, are relatively small. The normal limits were determined. The s. c. fasting lipids of blood do not occur in particulate form. Chylomicronæmia in infants and prematures were investigated after feedings of mother milk and various dilutions of cows milk.

The clinical significance and reliability of the method have been discussed from some of our studies.

On the pyruvic acid content in the blood of healty children

by

Hans Tallqvist, *Finland*

Pyruvic acid is an important product in aerobic as well as in anaerobic carbohydrate metabolism. The pyruvic acid was determined on the blood of fullterm and premature infants, in the umbilical artery and vein blood at parturation, and from umbilical vein blood in cases of "sectio major" and "minor". The investigation shows that the pyruvic acid content decreases with the rising age and that the level is considerably higher during the first year of life in prematures than in full-term infants. The mean value in prematurely born individuals remains higher up to the age of forty years than in the full-term group. The mean value of the pyruvic acid is higher in the umbilical artery than in the umbilical vein. The mean of the pyruvic acid values at the end of gestation is higher than the corresponding figure at an early period of gestation. The results are interpreted as being related to the fetal capacity for anaerobic metabolism, in both the premature and the full-term newborn, and in some cases indicating a persistent change in the orgànism's enzymatic system.

DISCUSSION

OLUF ANDERSEN, *Denmark*

Andersen pointed out that in evaluating the results of analyses of blood from the umbilical artery and vein, the rise in the pyruvic acid content of the mother's blood as a result of labour must be taken into account.

B. VAHLQUIST, *Sweden*

In his interesting paper Dr. Tallquist mentioned that the pyruvic acid values in the blood do not always show a correlation to the infant's development, as judged by the birth weight. It may be of interest to note that in a different context there is reason to assume that the true degree of fetal development at birth is better reflected in certain chemical data than in the birth weight. Dr. Berfenstam, of Uppsala, has shown that the carbonic anhydrase values in the red blood cells are strikingly correlated to the fetal development as evaluated on menstrual data.

C. E. RÄIHÄ, *Finland*

The pyruvic acid content is higher in the umbilical artery than in the vein. Pyruvic acid is conveyed from the fetus to the mother, there to undergo metabolism. Parturition increases about fourfold the pyruvic acid in the mother.

H. TALLQUIST, *Finland*

According to Friedemann and his coworkers, the pyruvic acid content in the blood increases after strenuous exercise: they found higher values in experimentees who had run about for one minute. I have sought to eliminate this source of error, most of the tests having been taken in the forenoons, the adult experimentees in great part having done no other exercise than is involved in the tram or bus journey to the hospital.

T_m for PAH and glucose in premature infants

by

FOLKE TUDVAD and JØRGEN VESTERDAL, *Denmark*

It was demonstrated in 8 premature infants 19 to 135 days old, with birth weights ranging from 850 to 2 060 g, that the tubular reabsorption of glucose and the tubular excretion of para-aminohippurate increased with increasing inulin clearance. As inulin clearance in the same subject is corresponding to the diuresis, this finding demonstrates that the above mentioned parts of the tubular function are varying from moment to moment.

The inulin clearance /Tm ratio decreased with increasing age,

indicating that these parts of the tubular function are maturing at a faster rate than the glomerular function.

The maximal tubular excretion of PAH (Tm for PAH) and the maximal tubular reabsorption of glucose (Tm for glucose) are increasing with increasing age.

Total and extracellular body water in children during ACTH treatment

by

BENT FRIIS-HANSEN, FOLKE TUDVAD and JØRGEN VESTERDAL, *Denmark*

The spaces occupied by heavy water (total body water) and by inulin (extracellular space) and plasma volume (determined with T-1824) have been determined in children suffering from rheumatoid arthritis before and after ACTH-treatment.

The phase volumes were found to be within normal limits before treatment.

During ACTH treatment the following observations were made (Table):

1) The plasma volume was unchanged.

2) The extracellular space expanded by abt. 3 per cent of body weight.

3) The intracellular water decreased by abt. 4 % of body weight.

A shift of water was demonstrated to have taken place from the intracellular to the extracellular compartment.

DISCUSSION

P. W. BRÆSTRUP, *Denmark*

A few investigators have examined whether other methods of calculation would give a more constant figure for the tubular function. In particular one should bear in mind the calculated concentration of glucose and para-aminohippurate in reabsorbed fluid, and possibly the estimated threshold too.

F. TUDVAD, *Denmark*

Animal experiments have shown that the reabsorption of glucose occurs in a very limited section of the tubules, but that of water in a much larger section of the same, and that this reabsorption of water may vary, for instance, with changes in the salt content of the tubular fluid and with hormonal influence. Hence it may not be possible to determine the concentration of glucose in the reabsorbed fluid.

Table

Subject	Date	Weight kg	Height cm	Total body water		Extracellular space		Plasma volume		Intracellular volume	
				liter	per cent of wgt	liter	per cent of wgt	liter	per cent of wgt	liter	per cent of wgt
Normals:											
Co	17.3	31.4	135			4.54	14.4				
Ki	6.4	34.2	145	20.10	58.8	6.13	17.9			13.97	40.8
Pts with rheumatoid arthritis:											
Fi	20.1	24.4	136	16.33	67.0						
Bo	26.1	23.5	123	14.70	62.6						
Ly	18.11	25.0	129	14.18	56.7						
	9.5	24.7	131	13.88	56.2	3.87	15.8	1.56	6.3	10.01	40.5
	After ACTH treatment:										
	2.6	26.4	131	14.50	54.9	4.91	18.6	1.58	6.0	9.59	36.3
Li	10.5	29.4	145	14.97	51.0	4.77	16.3	2.15	7.3	10.20	34.7
	After ACTH treatment:										
	28.5	29.5	145	14.97	50.8	6.00	20.3	2.15	7.3	8.91	30.4

From the Pediatric Department of the University in Bergen, Barneklinikken, Bergen, Norway. Chief: Prof. Alfred Sundal

Morbus hæmolyticus neonatorum in one of dizygotic twins

Examinations of the duration of Rh antibody in the blood of both of them

by

ARNE KÅSS, *Norway*

An Rh negative woman, III para, gave birth to dizygotic twins Nov. 8, 1950. Her husband was Rh positive, and her second child had icterus gravis and died after four days, in 1949. Eight days before the delivery of the twins, her blood was found to contain a Rh antibody, titer 1:2 in saline and 1:64 in albumen (all serological investigations were performed at Gades Institute of Pathology, Bergen).

In umbilical vein blood from twin no. I was found: Hgb. 130 %, icterus index 9, Rh negative, Coombs' test negative, Rh antibody present with titer in saline 1:2, in albumin 1:64. In umbilical vein blood from twin no. II was found: Hgb. 93 %, icterus index 18, Rh positive, Coombs' test ++, Rh antibody, in saline 0, in albumin titer 1:8.

Twin no. II was given exchange transfusion and remained in good condition. Several titrations of serum antibody showed a gradual decrease of the incomplet antibody until at 6 weeks p. p. the antibody had disappeared. After 6 weeks p. p. a continued decrease of blood values (Hgb. and erythrocyt count) was demonstrated. Serial checks of the Coombs' test and titer of Rh antibody during the first weeks p. p. in erythroblstotic children does not seem to indicate whether or not there will be increasing anæmia (our experience on this point will be published later).

Twin no. I showed no hæmolytic disease during clinical observation of 6½ weeks. The serum of this child contained complete antibody with a titer of 1:2 26 days p. p. 37 days p. p. no complete antibody could be demonstrated. The incomplete antibody was present 26 days p. p. with the titer of 1:16 and remained at this strength till 11 weeks p. p. 16 weeks p. p. the incomplete antibody titer was 1:4.

It should be emphasized that the titers of antibody in twin no. I (Rh negative) were at the same level as those found in the blood of the mother a few days before delivery. This single observation seems to show that the antibody passed freely through the placenta and also seems to support the assertion[1] that prognosis in erythroblastotic children is innersely proportional to the difference between the titer of serumantibody in mother and child at birth.

From the Children's Clinic, Rikshospitalet, Oslo. Head: Professor Salomonsen; and the Children's Clinic, Bergen. Head: Professor Sundal

Red Blood Cell Diameters in Megaloblastic Anæmia in children Needing Continuous Treatment

by

Olga Imerslund, *Norway*

There is a group of idiopathic megaloblastic anæmias in children which, clinically and hematologically, closely resembles pernicious anæmia in adults. They react apparently in the same manner to the administration of liver, liver extract, vitamin B 12, and folic acid. If the antianæmic treatment is discontinued, the anæmia will recur. The writer has a series of nine children, followed up several years. In contrast to pernicious anæmia in adults, hydrochloric acid was found in the stomach. No neurologic symptoms were observed.

The writer studied in these patients the distribution of red blood cell diameters before and after treatment, as well as the prothrombin levels. All nine patients showed, before treatment and during relapses, asymmetrical curves with a wide distribution, as in pernicious anæmia. The average diameter was greater than normal. The plasma prothrombin, studied in three patients during relapses, showed vitamin K refractory hypoprothrombinemia, the prothrombin varying between 65 and 78 per cent. In only one of three patients studied after treatment with Pernami liver extract was the distribution curve normal; and only one — who had a pathologic distribution curve — showed a normal prothrombin index.

[1] L. K. Diamond, V. C. Vaughan III and F. H. Allan jr., Ped. 6:630:1950.

Following treatment with folic acid the distribution curves did not become normal and the hypoprothrombinemia persisted. One patient was treated with B_{12}. The distribution curve became normal, the prothrombinvalues remained low. This patient then received 100 Gm liver daily by mouth for four weeks, during which period the distribution of red blood cell diameters remained normal but the prothrombin index was not normalized.

The results of examinations after treatment of these patients diverge in part from those found after treatment of pernicious anæmia in adults. It has been shown by Owren (International Congress of Hematology, Buffalo, N.Y.) that in pernicious anæmia the prothrombin index rises to normal values following treatment with liver. Owren and Larsen have demonstrated persisting macrocytosis — up to 30—40 per cent of the erythrocytes — after treatment with vitamin B 12.

DISCUSSION

B. VAHLQUIST, *Sweden*

The progressive decrease of Rh antibodies passively acquired from the mother has recently been studied by Wiener (Fed. Proceedings, 1951). In two Rh negative infants he found a fall of 50 per cent in about four weeks. This is consistent with observations made with respect to other types of antibodies, e. g. the antidiphtheritic ones. Assuming the initial value in the antibody titer of the newborn infant to be known, it is therefore possible to predict what value may be expected at a certain age. We must take into account, however, that heterologous antibodies, e. g. in ordinary diphtheria serum, disappear considerably more rapidly than the homologous antibodies in, for instance, the serum of convalescence and gamma-globulin.

From the Pediatric Department, University in Bergen (Barneklinikken). Head: Professor Alfred Sundal, M.D.

Osteopetrosis
Clinical and post-mortem examination of two cases

by

ALFRED SUNDAL, *Bergen, Norway*

Since Albers-Schönberg in 1904 described Marmorknochenkrankheit, about 200 cases have been reported, including some cases where the osteosclerosis was secondary to blood diseases so that genuine forms are rare. The characteristics of Albers-Schönberg's

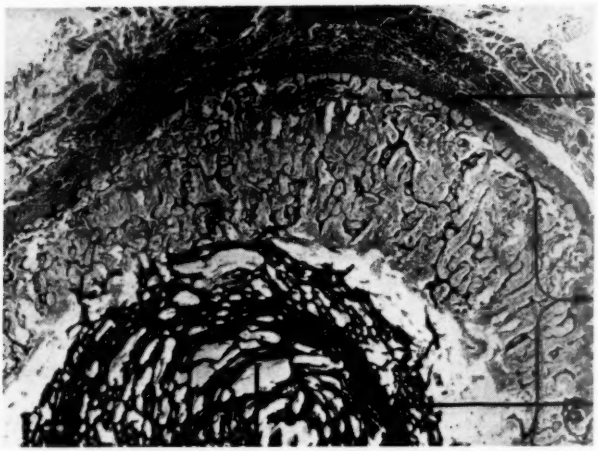


Fig. 1. Earlier bone marrow filled with chondroosteoid tissue with few narrow spaces.

disease (Marble bones, Osteosclerosis fragilis generalisata, Osteopetrosis, Chalky bones) are increased general density of the bones with increased content of calcium, disappearance of marrow cavity in the long bones, increased fragility and abnormal microscopic picture of the bones, further anæmi, thrombocytopenia, hepatomegaly, splenomegaly and general hyperplasy of the lymph nodes.

The author deals with two cases of osteopetrosis in two children in a family who had also two healthy children besides. There was no consanguinity between the parents. One infant came into the Children's Hospital in Bergen 1½ months old with severe anæmia, hepatomegaly, splenomegaly and a general but moderate enlargement of the lymph nodes. X-ray photograph of the skeleton showed a typical picture of Albers-Schönberg's disease with marked increased density of the whole skeleton without finer structure and without marrow cavity in the bone shafts. The child was treated for 3½ months in the hospital until his death 5 months old. The severe anæmia indicated in the whole 12 bloodtransfusions always with only shortlasting effect. No antibodies was found in the serum. Thrombocytopeni was noticed. At the age of 2½ months it developed a remarkable rosary of the ribs. Serum showed reduced phosphate,

Fig. 2. Patient P. S. 5 months. Femur. Periostealt newbuilded bone. No marrow cavity.

Fig. 3. Patient's sister. Femur. 10 years after death. Periostealt newbuilded bone. No marrow cavity.

slight dicreased calsium and increased alkalic phosphatase. Post-mortem examination at Gades Institute, Bergen, showed: General osteosclerosis in all bones without any marrow cavity. The earlier bone narrow cavity was filled with a condroosteoid tissue. Between the trabecels there were small marrow spaces partly filled with a few cells without hæmatopoesis, partly with chalky osteoid substance. In no place ordinary bone tissue were seen. In corticalis there were no signs of bone destruction or newbuilded bone. Between periost and corticalis there was considerable newbuilding of bone (Fig. 1) with large marrow spaces filled with cells and intense hæmatopoesis. This periostealbuilded bone contained plenty of osteoblasts, but no osteoklasts. The chondroosteoid junction of the ribs showed typical osteopetrotic changes of the bone, but also fractures in healing. These fractures were the only place in the skeleton

with about normal bone activity. Microscopic examination of the ribs showed no picture of rachitis.

The other child died 5 months old in 1940 — also with severe anæmia (not treated in hospital). Post-mortem examination of the bones 10 years after death, showed osteosclerotic bones without marrow cavity with abundant periosteal newbuilded bone (Fig. 3).

In this family two cases of osteopetrosis occurred. There was remarkable extramedullary hæmatopoesis in the subperiosteal newbuilded bone.

Metabolic disturbances in the skeleton in rickets

by

Rolf Zetterström, *Sweden*

Due to the constant reconstruction of bone tissue some parts of the bone undergoes dissolution. In these resorption processes the collagen bundles and the lime salts dissappear simultaneously. The resorption cavities thus formed are, sooner or later, filled by new Haversian systems.

In rickets the resorption processes seem to be much more intense than under normal conditions. The destruction of the bone tissue cannot be due solely to a deficiency in ions necessary for calcification as the organic matrix becomes degenerative and undergoes necrosis long before there is any resorption of the mineral salts. The resorption of lime salts sets in when the organic matrix is completely destroyed. The resorption cavities in rickets also show evidences of new calcification. This calcification process, however, does not seem to be capable of producing a normal bone structure.

The significance of these findings will be discussed.

From the pediatric clinic, Lund, Sweden
Head: Professor S. Siwe

Effect of Vitamin D on the Metabolism of Radiocalcium in Rachitic Rats

by

BERTIL LINDQUIST, *Sweden*

The mode and site of action of vitamin D is still unknown despite extensive investigations during recent years by a number of researchers, who have approached the subject from different angles. The author has carried out some experiments with radiocalcium in an attempt to elucidate the effect of vitamin D on the metabolism of calcium in rachitic rats.

The effect of vitamin D upon the absorption of calcium was studied. Experiments were carried out in order to find the minimum dose of vitamin D necessary for maximal absorption of calcium, given by stomach tube. In rachitic rats there is a well established effect on the absorption of calcium when the vitamin was given only 12 hours before Ca^{45}. The maximum effect of vitamin D on the absorption was noted 60—72 hours after administration. The effect was present 1 hour after the Ca^{45} was given.

In an endeavour to study the effect to vitamin D on the calcification mechanism a series of experiments were carried out in which a solution of Ca^{45} was given subcutaneously. The results indicate that vitamin D in some manner promotes mineralisation in rachitic bone. Futhermore, observations made in the present investigation suggest that not only bone formation but also bone resorption is increased during the healing phase of rickets. The uptake of Ca^{45} in the metaphyses with different doses of vitamin D gives a curve of response which may be used for testing vitamin D.

DISCUSSION

C. E. RÄIHÄ, *Finland*

Together with Forsander we have made some observations which have an interesting bearing on papers 27 and 28. We have investigated the effect of vitamin D on the formation of co-carboxylase (figs. 1—6). Vitamin D activates the phosphorylation of vitamin B 1, and it seems to us that this is correlated to age, so that the need of activation will be more pronounced in aging persons.

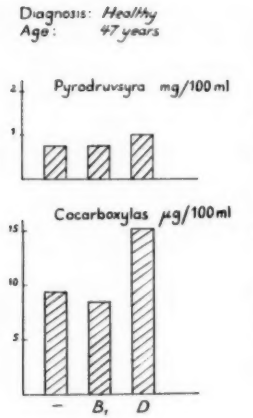


Fig. 1.

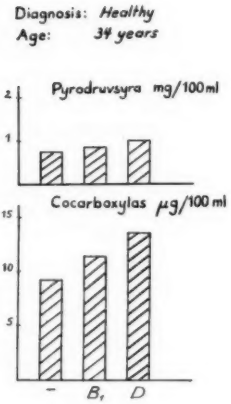


Fig. 2.

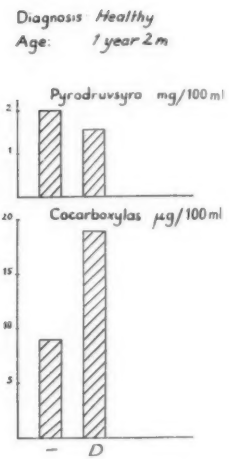


Fig. 3.

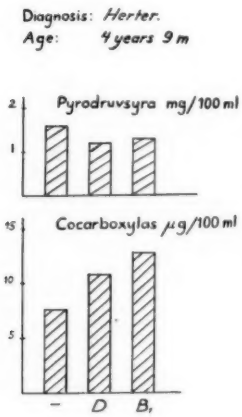


Fig. 4.

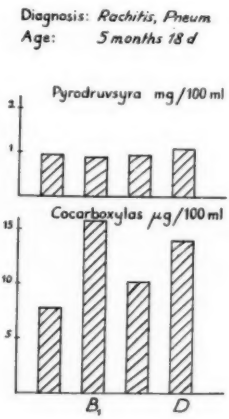


Fig. 5.

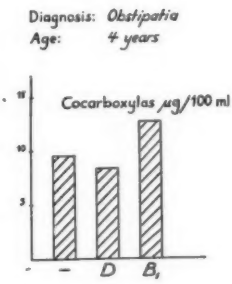


Fig. 6.

From the Children's Hospital Martinsvej, Copenhagen, Head: E. Winge Flensborg, M.D., and the Children's Hospital of Gothenburg, Head: Yngve Åkerrén, M.D.

Type Distribution in Cong. Malformation of the Heart in Early Life (0—3 years) compared with the Abbott 1 000 patient group

by

IB BOESEN, *Denmark*, and S. VENDEL, *Sweden*

About 700 cases of congenital malformation of the heart have been compiled from autopsies performed on children, deceased during the first year of life or, exceptionally, the 2nd or 3rd year. Only two percent were found among still-born children, and only few more after the first year. About 95 % died during the first year of life, ¾ of these before 3 months' age.

The case reports were analysed according to their anatomical type, and the type distribution compared with that found by M. Abbott in her group of 1 000 cases, selected from all ages. It is obvious that one may except to find quite another distribution of clinical-anatomical types among our 700 cases; this group was selected, so to speak by nature, according to the possibility of adjusting the abnormal circulation to the demands of active life. Certain types predominate: greater septal defects; double-shunts of special interest because of a special stress on the circulation; the hypoplastic conditions of the left half of heart associated with underdevelopment of aorta ascendens, a type rarely seen in older age but common in this group, 12 % of all cases.

The second aim of investigation has been to determine frequency of missed diagnosis in malformations of heart dying before "operable age", or the percentage of cases where suspicion may have risen before death but such diagnostic aids as X-ray and ecg were not used. In 25 cases of transposition dying neonatally, X-ray was never attempted. In coarctation of the aorta, infantile type, a suspicion of malformation arose leading to X-ray examination in only 30 percent. In Fallot cases, stenosis of the pulmonary artery and atretic tricuspid valves, half of all the patients never had an X-ray performed and so missed any chance to have a correct

diagnosis made, this fact is of practical importance. A considerably more intense diagnostic investigation of all suspect cases in infancy may well lead to increased possibilities for surgical aid.

DISCUSSION

E. MANNHEIMER, *Sweden*

The post-mortem examinations in cases of congenital heart disease in early infancy are often very difficult to perform. In the authors survey therefore a certain percentage of the diagnoses are suspected to be incorrect. Especially trained pathologists should make these examinations, if possible. If this is impossible the heart specimens should be spared and sent to the clinic where pediatric cardiology is represented as a speciality.

I quite agree with Dr. Vendel that many severe cases should be operated upon as early as possible. Anæsthesia problems no longer exist since intubation can be made without difficulty also in the newborn. Dr. Ekström at Kronprinsessan Lovisas Children's Hospital in Stockholm has already operated upon several cases of patent ductus arteriosus and vascular anomalies under one year of age.

There are many cases of congenital heart disease which can only be diagnosed before death, e. g. mild cases of isolated pulmonary stenosis. Therefore both clinical and post-mortem examinations must be made in order to establish a correct diagnosis.

J. LIND and C. WEGELIUS, *Sweden*

In no less than 70 per cent of the series here presented, death occurred prior to the age of three months. It is therefore of prime importance to establish the diagnosis as early as possible, in which connection, we are thinking of the possibility of establishing the diagnosis at the maternity hospital itself, as most the infants are examined there by a pediatrician. During the first week of life, however, the diagnosis presents formidable difficulties. In newborns the general symptomatology is so vague that often it does not even suggest cardiac disease. Auscultation does not provide any effective guidance, since murmurs during this period of life are not tantamount to cardiac disorder; they may be due to a reversible functional circulatory disturbance. Also the absence of murmurs does not rule out a congenital heart defect. Cardiograms often reveal enlargement of the heart during this period of circulatory adjustment, without any organic heart defect necessarily being present. For instance, we have often seen transient enlargement of the heart in association with atelectases. The electrocardiogram too is difficult to evaluate, in that it presents changes which are normal in the newborn but which are ascribed pathologic significance in older children. With regard to more advanced methods of examination, catheterization of the heart is at present virtually impracticable in such small infants. Angiocardiography, on the other hand, can readily be done and, to judge by our experience, which is based on about fifty cases, does not involve any greater risks in the newborn than in older children. Further, in these small infants one obtains very clear pictures with

a good contrast effect. The dose of contrast medium (Astra umbradil 70 per cent) in our series was 1 to 1½ ml per kg body weight. However, the angiocardiographic method employed must satisfy certain requirements if it is to yield satisfactory results. In view of the exceptionally rapid heart rate, a very high speed must be used so that the heart function, and not merely its anatomy, can be evaluated. Moreover, if we are to be able to follow exactly the passage of the contrast medium through the heart and to judge the localization and size of any abnormal communications that may be present, the roentgenograms must be taken in two planes.

Our experience shows that with this method congenital heart defects can be diagnosed, even during the newborn period, in majority of the cases.

S. VENDEL, *Sweden*

In reply to Dr. Mannheimer's remarks I would like to point out that we fully realize the major sources of error that must be anticipated when a series is collected, is this has been, from all corners of Scandinavia. And perhaps I may take this opportunity to emphasize the very great desirability, at all hospitals in Denmark, Norway and Sweden, of having deformed hearts autopsied by special pathologists, so that during the next five to ten years no heart may be lost to the work of research.

We must take the present series such as it is, but if the above suggestion should be followed we might in the next few years obtain just as reliable a series as we could wish for.

I can fully subscribe to Mannheimer's remark that if there is no possibility of sending hearts to a special pathologist, then it would be most desirable to preserve every abnormal cardiac specimen, so that there *might be a possibility* later of studying the specimens.

From the school health department of Oslo, School medical headofficer: Dr. med. L. Stoltenberg

Judgement of the growth of children with a diagram, after a "grid-method"

by

ALF ÖDEGÅRD, *Norway*

The evaluation of the growthdevelopment of children is of importance in determining if they are thriving. To-day the growth of children is judged by comparing the weight and height relationship with figures from a standard which indicates the weight and height of the average child. This comparison is not practicable and does not permit a right conclusion.

The study attempts to show that the weight and height projections

of a child may be marked down in a plan and let this point develop in time in a 3-dimensional room. The course of this line may be registered on a diagram, in relation to the development of the average child and to the extreme values in weight and height (Fig. 1—3).

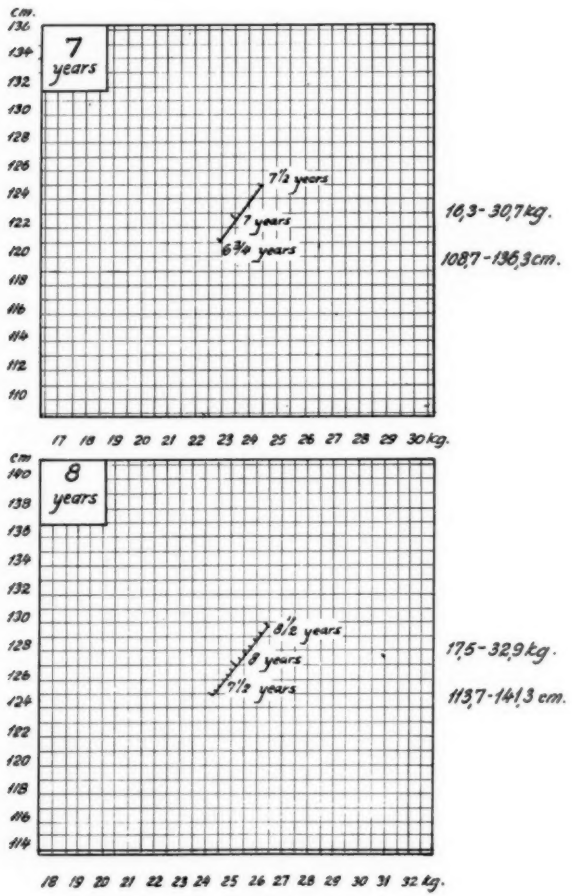


Fig. 1.

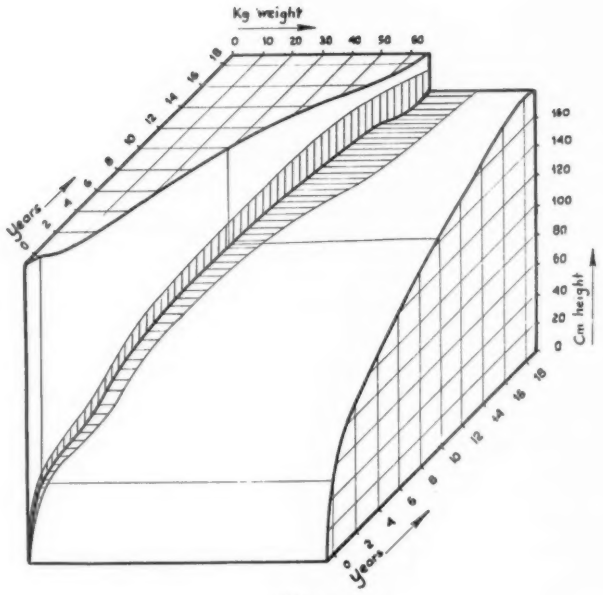

Kg weight
0 10 20 30 40 50 60
0 2 4 6 8 10 12 14 16 18
Years
160
140
120
100
80
60
40
20
0
Cm height
0 2 4 6 8 10 12 14 16 18
Years

Fig. 2.

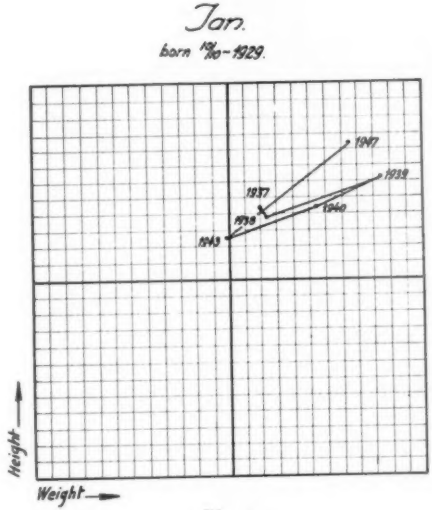

Jan.
born 18/10-1929.
1947
1939
1937
1940
1938
1943
Height
Weight

Fig. 3.

From the diagram one can determine whether or not the development has been regular acceleration of weight or height in the measured period.

DISCUSSION

W. OLSON, *Norway*

As a brief illustration to Dr. Ødegård's paper I would like to demonstrate a few photographs of a girl who is at present hospitalized in our department (Department of Child Psychiatry, Oslo). She is twelve years old, and her height and weight on admission were 156 cm and 29 kg respectively. According to the usual evaluation her weight was below normal, but on comparison with the Lichtenstein-Dahlberg-Broman table it was found to be within the normal range, which for a height of 156 cm in girls is 46.4 ± 16.

The photographs demonstrate clearly the need to consider factors other than height and weight — perhaps not least the constitutional factors.

P. KARLBERG, *Sweden*

In evaluating bodily development we in Sweden use the standard tables of Broman, Dahlberg and Lichtenstein. Since they give the relation of height to age, it is possible to tell whether the child is too tall or too short for its age. They show too the relation of weight to height, which gives an idea of whether the child is thin or fat — i. e., an idea of the physical constitution.

The tables embrace the ages of 1 to 20 years. For infants we use as a rule von Sydow's values for weight and age in children with different birth weights. Here we obtain a combination of the height factor and the constitutional factor, which means that we get the same value for a short and fat child as for a tall and thin child.

At Nortull Hospital we have taken several different body measurements in healthy children between the ages of 2 weeks and 24 months. From these measurements we have calculated the relations between height and age and weight and height in infants too. In children aged from 12 to 24 months these measurements are consistent with the values given by Broman, Dahlberg and Lichtenstein. By combining these two series the relations between height and age and weight and height were obtained for ages ranging from two weeks to adult ages, and on the resulting data was based a proposal for a Swedish "grid". Such a grid should facilitate more than tables can do the evalution of the actual bodily development of a child, and should provide better possibilities of following the development at subsequent examinations. Te "Grid" is being worked out with Dr. S. Iggbom and will be published in Acta Pædiatrica.

From the State Serum Institute, Copenhagen
Chief: J. Ørskov, M.D.

On the occurrence of Escherichia coli 55: B5: 6 and E. coli 111: B4 in fæcal samples from infants with diarrhœal disease, and in a control material

by

ANNALISE DUPONT, *Denmark*

In the period 1 April 1950—1 April 1951 all fæcal samples of children under 1 year of age received by the State Serum Institute, Copenhagen, 3 104 in all, were examined for E. coli 55 : B5 : 6 and E. coli 111 : B4 by means of slide agglutination. (This department performs all examinations, from the whole country, for the presence of pathogenic intestinal bacteria.)

While E. coli 111 : B4 has not occurred the last 10 months, E. coli 55 : B5 : 6 was present rather frequently throughout the period. The positive cultures were from cases of diarrhœa occurring in small outbreaks in various institutions for children, including pediatric wards in Copenhagen. Moreover, a number of children of all ages who were cared for by the same nursing staff had the same type E. coli in the stools, whereas attempts to find these types in cultures from the nursing staff (fæcal samples as well as nose and throat swabbings) were negative with one exception.

The control material consisted of 3 168 fæcal samples, divided into 4 groups:

1. Anal swabs from newborns, taken immediately before the discharge from the lying-in hospital of Rigshospitalet, Copenhagen; 538 samples, all of which were negative.

2. 940 samples from healthy children under 1 year, received from 12 public health nurses. All samples were negative.

3. 1 412 anal swabs from children of all ages with non-diarrhœal diseases, taken on admission to and at discharge from the Children's Hospital, Martinsvej, Copenhagen. All samples were negative with one exception.

4. 278 fæcal samples from 25 children's homes in all parts of the contry. All samples were negative.

DISCUSSION

J. A. GRÖNROOS, *Finland*

At the spring meeting of the Finnish Pediatric Association in 1950 and the Ninth Scandinavian Congress of Pathologists between 19th and 21st June, 1950, I described, in a preliminary report, the occurrence of *Escherichia coli* O 111 : B 4 : H — (D433) in Åbo. The investigation continued at the Turun Yliopisto Children's Clinic and at the Bacteriological Laboratory of the same university. During the latter part of 1950 a total of 1 740 fecal samples were taken from 461 infants and studied for the presence of the aforementioned bacterium. Two hundred and thirty-one cases presented symptoms of gastro-dyspepsia or gastro-enteritis, the conditions varying from slight dyspepsia to a state of intoxication. The control group comprised 230 patients hospitalized in the same department under varying diagnoses, but showing no symptoms of gastro-dyspepsia. In the gastro-dyspepsia group, 45 cases showed positive fecal tests — in most of them more than once. Since 1950 the samples have also been studied for the presence of the *E. coli* strain with the antigen formula 55 : 5 : 6, the results being negative throughout.

The control group included a total of five positive cases, though in them the tests were only occasionally positive. No signs of gastro-dyspepsia were present.

Widal cultures were done in ten cases, with negative results.

During the latter half of 1950, 532 pharyngeal swabs from the two groups were examined. *E. coli* 111 : 4 : — was cultured in seven of the positive cases, from the pharynx too.

The higher incidence of positive cases in the gastro-enteritis group suggests that this strain of *E. coli* might be regarded as an etiologic factor to be reckoned with in gastro-enteritis. The strain with the antigen formula 55 : 5 : 6, which preponderated in Dr. Dupont's series, indicates that there probably exist undiscovered *E. coli* strains which have other antigen formulas and which give rise to gastro-enteritis.

From the Children's Clinic of Helsinki University
Chief: Professor Arvo Ylppö

On Calcium Metabolism in Interstitial Plasma Cell Pneumonia in Infants

by

NIILO HALLMAN, *Finland*

On the basis of renal changes in interstitial plasma cell pneumonia the calcium content in 6 cases (Table 1) and the balance of calcium and phosphorus in 1 case (Table 2) have been investigated during the acute stage of the disease and also afterwards when the patients state of health had returned almost to normal. In each case the plasma

Table 1

Case	Days after the beginning of dyspnoe	Dyspnoe	Plasma		Alk. fosfatas
			Ca mg %	P	
1	2	+	16.0	—	—
	3	+	20.8	—	—
	6	+	21.0	—	—
	10	+	17.4	1.5	8
	24	—	12.3	4.1	10
	35	—	11.4	5.6	13
2	1	+	20.3	—	—
	4	+	17.5	4.6	—
	10	±	12.9	2.9	—
	16	—	10.3	—	—
3	2	+	16.5	4.8	—
	6	+	18.8	4.1	—
	17	±	12.7	3.9	—
	39	—	10.8	3.6	—
4	6	+	17.8	5.2	13
	10	+	15.6	—	—
	28	—	12.2	7.4	—
5	5	+	19.7	3.6	7
	8	+	18.2	—	5
	9	Exitus letalis			
6	5	+	16.0	3.6	11
	10	Exitus letalis			

calcium increased markedly during respiratory difficulties, the highest figures varying between 16.0—21.0 mg %. In the 4 patients, who recovered, these values decreased to normal simultaneously with the disappearance of the respiratory difficulties. In those patients who died these values remained high. The balance tests in the acute stage of disease showed an increased urinary excretion of calcium

Table 2

Date	Urine		Plasma	
	Ca mg	P mg	Ca mg %	P mg %
16.X.	54	138	16.5	4.8
17.X.	51	112		
18.X.	60	101		
19.X.	75	75	18.8	4.1
22.X.	12	18	10.8	3.6
23.X.	12	19		
24.X.	13	13		
25.X.	9	17	10.5	4.1

and phosphorus. Simultaneously with the increase of the plasma calcium the inorganic phosphorus of plasma decreased slightly but the alkaline phosphatase remained normal. No considerable deviations from normal values in plasma chlorides, bicarbonate content, potassium, sodium and magnesium and in the sodium and potassium in the red blood cells could be shown. The plasma proteins decreased slightly and an increase of the γ-globulin in the electrofores was noticed.

From the Ullevål Hospital, Department of Pediatrics
Head: Roald Rinvik, M.D.

Pneumonia Therapy at the Ullevål Hospital during the year 1950/51

by

ROLF REILER, *Norway*

The author studied the pneumonia material of the Ullevål Hospital, Department of Pediatrics, for the year 1950/51. An investigation was carried out comparing the effect of large doses of sulfonamides, penicillin, aureomycin, and combined treatment, on the course of disease in various age groups.

DISCUSSION

C. FRIDERICHSEN, *Denmark*

In view of the good results we had obtained with single large doses of sulfathiazole in the treatment of pneumonia, we commenced, on January 1, 1950, the administration of *single large doses of procaine penicillin* according to the following scheme:

0—1 year:	200 000 units
1—6 years:	300 000 units
over 6 years:	400 000 units

In 1950 we had 98 cases of pneumonia, including 34 of virus etiology which did not come under this treatment. The age incidence was as follows:

Sixteen patients	from 0 to 12 months	No deaths
Twenty-two „	„ 1 „ 2 years	
Twenty-three „	over 6 years	

The temperature fell to normal within 12 to 48 hours. The pulse and respiration became normal a few days later. Two patients were in such poor condition that the dose of procaine penicillin had to be repeated the following day. In cases where otitis supervened, continuous penicillin treatment was resorted to. Eight patients showed a secondary rise in temperature from 2 to 6 days after the start of treatment, but the fever subsided spontaneously.

To secure as large a series as possible combined with a control series, we started, on January 1, 1951, team work with five other children's clinics in Copenhagen. Patients admitted on the same dates received single large doses of procaine penicillin according to the above scheme; patients admitted on different dates received continuous treatment consisting in two injections daily of sodium penicillin according to the scheme reported by Jersild for the treatment of scarlatina (Lancet, 1948). We hope within the course of two years to have about a thousand cases with five hundred in each group. The disease is most dangerous in the 0—6 years age group, and a large series is therefore essential.

At present I can recommend procaine penicillin treatment in single large doses, which is more convenient and less expensive. The fall in temperature is not so striking as it is in treatment with single large doses of sulfathiazole; it occurs somewhat later, just as the clinical symptoms subside somewhat more slowly. None the less, the single injection of procaine penicillin has its practical advantages both for the patient and for the family's finances.

Y. ÅKERRÉN, *Sweden*

Åkerrén stressed the importance of symptomatic therapy parallel with the causal treatment directed against the infection. The majority of deaths occur within 24 hours of admission, i. e., before the specific treatment has had time to act. At Gothenburg Children's Hospital we use, especially in cases of the capillary bronchitis type, warm mustard baths (39°—40° C) followed

by affusion with cooler water (25°—27° C). The salutary effect is manifested not only in a better skin color and more effective respiratory movements, but often in energetic coughing too, which helps to remove obstructing matter from the air passages. We frequently use too, in infants, serum or blood transfusions (15 ml to a maximum of 20 ml per kg body weight) combined with intravenous injection of hypertone (25 per cent) glucose solution in doses of 10—15 (—20) ml. This has both a nutritive effect and an osmotic action on the respiratory tract congestion. It is important that the intravenous injections be given slowly (at the most 5 ml, or in severe cases 2—3 ml per minute), a careful watch at the same time being kept on the patient's condition and reaction.

From the Epidemic and Pediatric Department, Ullevål Hospital, Oslo
Chiefs: Peter M. Holst, M.D., and Roald Rinvik, M.D.

Late sequelæ of Hemophilus influenzæ meningitis

Investigation of 32 cases

by

SVERRE HESTETUN, *Norway*

An investigation has been made of 32 patients with *Hemophilus influenzæ* meningitis admitted to the Epidemic Department, Ullevål Hospital, during the 10-year period 1940—1949 incl. Eleven of these died of the disease, but the deaths occurred especially in the first years, when the treatment was less systematic and before streptomycin was used. The prognosis was poorest in the youngest patients, those admitted late in the illness, and those who on admission presented neurological signs, such as convulsions and palsies. The sugar content of the cerebrospinal fluid was generally lower in the patients who died, but there was no correlation between the cell number in the C.S.F. and the prognosis.

Of the 21 surviving patients 2 could not be followed up, but these were ostensibly in good health. The remaining 19 have been submitted to follow-up examinations in the Ullevål Hospital, in special departments for otorhinolaryngology, neurology, by electro-encephalography (EEG), as well as psychiatry (examined by O. Bjordal, M.D.). The average age of those patients at the onset of meningitis was 2 years 4 months. The follow-up took place on an average 3 years and 10 months after the admission (ranging from 11 months to 10 years and 6 months). Seven of these 19 patients

Results in Nineteen Followed Up Cases of Hæmophilus Influenzæ Meningitis

Number of Patients	Neurol. Sequelæ	Eeg Sequelæ	Vestibul. Sequelæ	Cochlear Sequelæ	Psychic Sequelæ	Invalidity
8	—	—	—	—	—	—
5	—	Slight	—	—	—	—
1	—	Slight	Bilat.	—	—	—
1	—	—	Bilat.	—	—	—
1	—	Slight	Bilat.	Unilat.	—	Minor degree
1	—	—	Bilat.	Unilat.	—	Minor degree
1	—	—	—	Bilat.	—	Major degree
1	Spastic Hemipares.	Severe	—	—	?	Major degree
Total	1	8	4	3	1	4

had been treated with sulfonamides alone, while in the remaining cases this was combined with streptomycin.

Of the 19 patients followed up 8 had no demonstrable sequelæ (Table). In 5 slight changes in the EEG were the only positive findings. The remaining 6 presented slight to massive morbid clinical changes.

Loss of vestibular function was found in 4 patients, but seemed to be of no practical importance, and Romberg's test was negative in all 4 cases. Impaired hearing was observed in 3 patients, in 2 unilateral, and in the 3rd bilateral (speaking voice heard at 1 m.). Two of the patients with abolished vestibular function, of whom

one had unilateral impaired hearing, also showed slight changes in the EEG.

One patient had severer sequelæ with spastic hemiparesis of the right extremities. The EEG showed considerable abnormalities localized chiefly in the left hemisphere. The result of the psychiatric examination showed that she (3 years 4 months old) was backward in speaking, and that her intellect was at the lower limit of normal. Her I.Q. could not be determined exactly. As for the remaining 18 patients conversations with the parents and examinations of the patients themselves revealed no psychopathological traits. I.Q:s according to Terman and Merrill's test, were found to range from about 100 to 132 (average 113.8).

Damage due to streptomycin may have been present in three patients with loss of vestibular function, including one who also had unilateral impaired hearing.

The morbid anatomical conditions underlying the sequelæ have been discussed.

A more detailed account of these investigations will be published in Norwegian in Nordisk Medicin.

DISCUSSION

B. HAHN, *Sweden*

I would like to describe briefly the cases of *Hemophilus influenzæ* meningitis that were treated at the Crown Princess Lovisa's Children's Hospital during approximately the period embraced by Dr. Hestetun's investigations.

They totalled 11, of which five were treated with sulfonamides alone and the other six with sulfonamides and streptomycin. Five of the patients were infants, four were aged between one and two years, and the remaining two were aged four and seven years respectivly.

Of the five treated with sulfonamides alone, three died, including two infants and one child of 13 months. One death occurred within 24 hours of admission after five days' illness at home. The other two occurred at three and one and a half weeks respectively after admission; one came under treatment at a late stage and had early shown symptoms of occlusion; the other had the lowest dose of sulfonamides in that group — 8 cg per kg body weight per day. The two survivors were both aged two years, and each came under treatment at an early stage. — One of them showed a very turbulent and protracted course, with positive *H. influenzæ* cultures over a long period. The dose was low — 9 cg per kg body weight per day. Ultimately the patient showed every sign of full recovery, but later an appreciable impairment of hearing developed. At the last follow-up he could only hear

the spoken voice at 3 meters, and was totally deaf in one ear. The vestibular function was completely absent, but he showed no signs of this disturbed function. His speech development had been very late, the speech not being pure until he was eight. He had an I.Q. (Terman-Merrill test) of 81 at seven years and of 85 recently at the age of fourteen. The EEG was normal and there were no demonstrable neurologic disturbances. — The other survivor had a much less turbulent course and recovered in two weeks, the dose being 17 cg per kilogram. She now shows no signs of clinical sequelæ.

On considering the dosages here in the light of our present experience, it is clear that they were comparatively low, being around 10 cg per kg body weight per day in several cases. Roughly double that dosage is considered necessary today.

All of the patients who received combined treatment survived. Five of them came under treatment early, healed in one to two weeks, and now show no clinical sequelæ with respect to hearing, balance, neurologic status, and intellectual development. The EEG is normal in three cases and reveals slight changes in one; the fifth has not attended the clinic for electroencephalographic examination.

The sixth case in which combined treatment was given — a girl of 18 months — came under treatment five days after the onset. Two weeks later she was afebrile and had virtually normal spinal fluid, but was totally deaf, with completely absent vestibular function and paresis of the abducens. At the last follow-up three and a half years later, these sequelæ still persisted, with the exception of the paresis. The patient now has disturbances of balance, being apt to stumble and fall, but Romberg's test is negative. She attends a school for deaf mutes. No intelligence test has been possible, but she learns readily and appears to be of normal talent. Her EEG shows slight dysrhythmia, and the neurologic findings are negative.

The duration of streptomycin treatment varied between 10 and 15 days. In no case other than the last-mentioned was the vestibular function found to be affected during or immediately after treatment or at recent follow-ups.

Of the eight healed cases, two have severe sequelæ and the other six appear to be quite healthy. The fatal cases and those with sequelæ occurred in patients who came under treatment at a late stage, or in whom the treatment was inadequate.

The Results of the Treatment of Tuberculous Meningitis at the Children's Clinic, Helsingfors

by

OLE WASZ-HÖCKERT, *Finland*

Sixty cases of tuberculous meningitis has been treated with Streptomycin and PAS during two years at the Children's Clinic. The same principles have been used as by Bebré, with some principles from Cocchi. Neuro-surgical assistance has been used.

Thirty children have been discharged as cured and 30 have died. The mortality rate is 50 %. The percentage of patients too-late-admitted is high in the material.

Age distribution:	0—1 year:	10
	1—4 „ :	29
	4—7 „ :	15
	7— „ :	5
Frequency of blockage:	high-blocks:	24
	low-blocks:	17
Observation time:	6—18 months after the end of the treatment	

Some clinical and practical points were discussed.

DISCUSSION

K.-A. MELIN, *Sweden*

I would like to make a few comments on Dr. Wasz-Höckert's paper. The first is purely a question of nomenclature. Would it not be better if we in general substituted the term "tuberculous meningoencephalitis" for "tuberculous meningitis". In these cases, as in other infections in the central nervous system, there is unquestionably involvement of the brain too, and not the meninges alone. One of our cases at the Kronprinsessan Lovisa's Children's Hospital — a little girl who died — had very severe tuberculous encephalitis with tuberculous changes throughout the cerebral cortex.

Further, I would emphasize the value of serial EEG's for following the course of the disease. Electroencephalography, along with other examinations, will often give a good idea of the course, as is evident from the adjoining curves (figs. 1 and 2) from two cases.

The greatest caution must be observed in evaluating healing. This is perhaps illustrated by the following, which happened at last year's annual congress of the *Deutsche Gesellschaft für Kinderheilkunde*. A paper on the late condition in 20 cases of tubercular meningoencephalitis which had been symptom free for over two years was submitted in July. When the paper was read in September, only 14 of them remained, the other six had having recurrences.

I can subscribe to Dr. Wasz-Höckert's statement that loss of the vestibular function entails but little discomfort. We had one patient who developed meningoencephalitis in infancy, before he had learnt to walk. Although his vestibular function was totally abolished, he learned to walk in normal time on recovering, and now has no difficulty in keeping his balance even when walking in the dark.

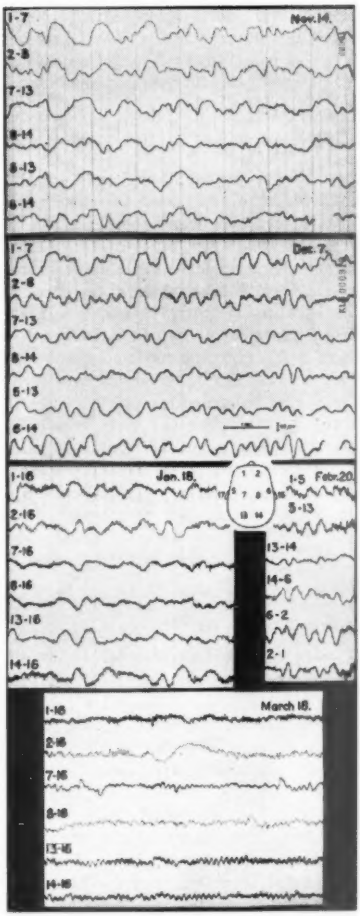

1-7
Nov. 14.
2-8
7-13
8-14
5-13
6-14
1-7
Dec. 7.
2-8
7-13
8-14
5-13
6-14
1-16
Jan. 18.
1-5 Febr. 20.
2-16
5-13
7-16
13-14
8-16
14-6
13-16
6-2
14-16
2-1
March 18.
1-16
2-16
7-16
8-16
13-16
14-16

Fig. 1.

In conclusion I would merely enquire whether the Finnish patients were submitted to intelligence tests. Of our five patients who have been symptom free for a considerable time, four have normal intelligence according to Terman-Merrill tests. Only in one case, a seven-year-old boy, has the I.Q. shown a slight fall (95 to 86). Finally I would emphasize the importance of occupational therapy, especially in the younger ones among these patients.

G. HERLITZ, *Sweden*

I would like to ask Wasz-Höckert whether hospitals in Finland or the Scandinavian countries yet have any major experience of combined treatment including promizole in tuberculous meningoencephalitis. Since Edith Lincoln introduced the method some years ago, other investigations have been reported, including one from Shanghai, which seem to confirm the good results obtained in America. I myself have little experience of streptomycin, for tubercular meningoencephalitis is fairly rare in my part of Sweden; but I have tried the combined treatment in two cases of the disease which we have encountered during the past year. The promizole was not easy to obtain, but the amount placed at our disposal sufficed for treatment according to Lincoln's method. In one case, a nine-year-old boy, the treatment has been completed; in the other, a five-year-old girl, it is still proceeding. After eight months the boy now has a virtually normal spinal fluid cell count and is symptom free in other respects. The girl now shows, after three months treatment, a considerable clinical improvement. We have not observed any of the characteristic toxic side-effects of promizole. Vestibular damage has occurred but its onset was very late — after seven to eight months' treatment with streptomycin in the case that has the longest follow-up period.

ARNE KÄSS, *Norway*

In 1948 a six-year-old boy with tubercular meningitis was treated for three months with streptomycin intramuscularly and intraspinally. At the conclusion of treatment the spinal fluid showed a slight increase in cells and protein which was ascribed to the treatment, but otherwise there was no sign of disease either then or during the next few months.

Nine months after the completion of treatment the patient had a recurrence, and streptomycin-sensitive tubercle bacilli (inhibition of growth by 10 μg per ml streptomycin) were found in the spinal fluid. He was now submitted to six months' treatment with dihydrostreptomycin-streptomycin intramuscularly and intraspinally, this time combined with PAS. Shortly after this treatment the spinal fluid was found to be normal and the general condition good.

At a follow-up 19 months after the conclusion of treatment the vestibular function was totally absent, but otherwise there were no signs of mental or physical sequelæ.

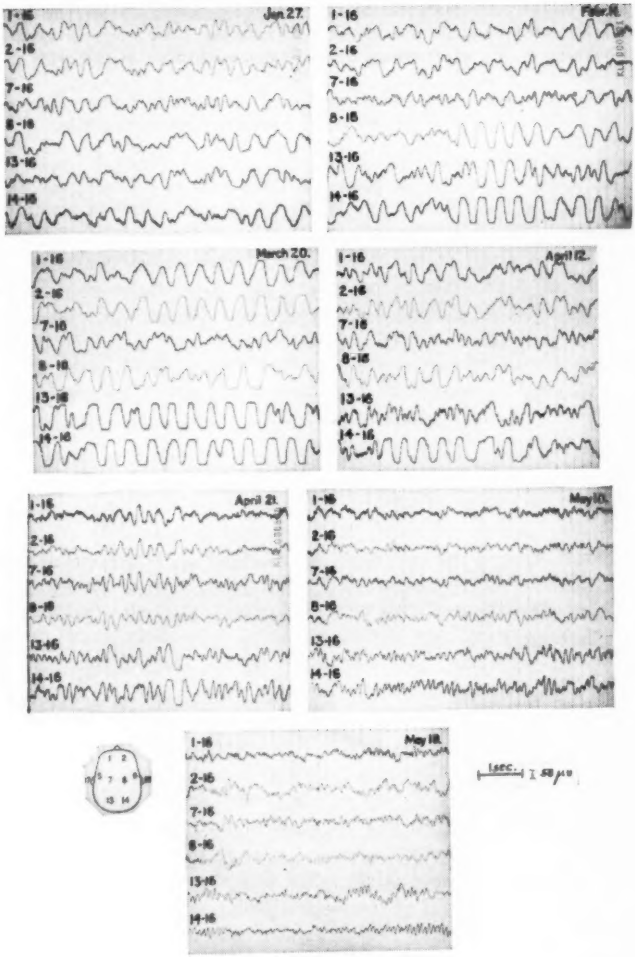

1-16
Jan 27.
2-16
7-16
8-16
13-16
14-16
1-16
Feb. 16.
2-16
7-16
8-16
13-16
14-16
1-16
March 20.
2-16
7-16
8-16
13-16
14-16
1-16
April 12.
2-16
7-16
8-16
13-16
14-16
1-16
April 21.
2-16
7-16
8-16
13-16
14-16
1-16
May 10.
2-16
7-16
8-16
13-16
14-16
1-16
May 18.
2-16
7-16
8-16
13-16
14-16
1 2
3 7 8
13 14
1 sec.
50 μv

Fig. 2.

O. WASZ-HÖCKERT, *Finland*

To Dr. Melin: All cases were submitted to electroencephalography at the end of treatment, but, due to practical difficulties, only a few immediately after admission. My observations from Italy and France accord with those of Dr. Melin.

No I.Q: tests were made, since we lacked comparative values. The older children in the series have resumed their school studies successfully.

To Dr. Herlitz: Promizole is probably no more effective than other sulfons, which of course are good and often prevent the development of resistance.

We have not used promizole: partly because of the shortage of Dollars, and partly because we wanted to study the effect of streptomycin and PAS in a larger series.

From the Pediatric Clinic at Kronprinsessan Lovisas Children's Hospital, Stockholm, Head: Professor C. Gyllenswärd, and King Gustaf V:s Research Institute, Stockholm, Head: Professor Nanna Svartz

The influence of various remedies upon tubercle bacilli

by

H. ENELL, CHR. LINGEN, K.-A. MELIN and S. HEDMAN, *Sweden*

Clinical studies over the effect of diplomycin in treatment of cases of tuberculous meningoencephalitis seemed to show clinical amelioration that could be attributed to the use of this remedy. Further observations, primarily on animals, did not, however, give the same encouraging results. With bovine tubercle bacilli infected, nontreated rabbits all died within three weeks. Diplomycin treated such animals died within same period of time or lived in some cases up to one week longer. Streptomycin treated such rabbits live more than two months after infection, without any symptoms of tuberculous disease.

The influence of various remedies directly upon tubercle bacilli was studied with the aid of the electron microscope. A bovine strain in Dubos cultures of different ages was primarily studied. Streptomycin, paraaminosalicylic acid, conteben and diplomycin was later added to different cultures and the bacilli studied at various intervals. The different changes in the bacilli were compared and the results of this study are presented in microphotographs.

From the Pediatric Department of the Akademiska Sjukhuset, Uppsala, Sweden. Head: Professor B. Vahlquist

Triple vaccination in infancy

by

L. Hesselvik, and B. Vahlquist, *Sweden*

Several investigators in recent years have proved the possibility of successful vaccination of infants against diphtheria, tetanus and whooping-cough from the age of three months. Early immunization has definite advantages, the protection is established in the most susceptible age period and the psychic trauma is negligible. The use of triple vaccines makes possible simultaneous immunizations against all three diseases mentioned in one and the same injection.

On the 1st of January 1951, a special immunization clinic was started at the Pediatric Department of the Akademiska Sjukhuset, Uppsala. The triple vaccine used is manufactured by the Swedish State Bacteriological Laboratory. One milli-litre of the vaccine contains 12.5 flocculation units of diphtheria toxoid, 7.5 flocculation units of tetanus toxoid and 15 000 000 000 of whooping-cough microorganisms. The following schedule for immunizations is adopted: At birth (in the maternity ward) BCG-vaccination. At three months of age checking of the BCG immunization and the first injection of 1.0 ml of the triple vaccine. At four and a half months 1.0 ml of triple vaccine. At six months 1.0 ml of triple vaccine and, at the same time, smallpox vaccination.

It is our intention to restrict the triple vaccination to the three injections given during infancy and to postpone further "booster" doses until school age or to future epidemics of diphtheria or whooping-cough. Such a mode of action will not guarantee a permanent protection but rather a basic immunity, enabling the individual to immediate response to "booster" injections and probably sufficient in itself to assure protection against serious forms of the diseases in question.

In our present experience, founded upon about 600 injections of triple vaccine, more important side reactions have been practically non-existent. About 20 % of the infants get a rise in temperature to or slightly above 38 ° C the same or the following day. Only in

very rare instances have the mothers, however, noticed any influence upon the general condition of the child. Local reactions, defined as infiltrations exceeding 10 × 10 mm in size, are shown by about 30 % on the third day after injection. When checked six weeks later these infiltrations have disappeared with very few exceptions. Ulcerations or abscess formations have not been observed.

The effect of the vaccination, carried out as outlined above, has hitherto been tested in a limited material only. 2—4 weeks after the last injection, however, 22 children investigated showed serum antibodies against diphtheria ranging from 0.5 to 13.5 IE/ml, and against tetanus exceeding 0.1 IE/ml in every case. These results can be regarded as fully satisfactory.

The treatment of acute rheumatic fever with ACTH and Cortisone

by

Bengt Jonsson, *Sweden*

The published reports indicate that ACTH and Cortisone are useful in acute rheumatic fever, as judged from their effect on the general condition, joint symptons, fever and sedimentation rate. The effect of these drugs upon the cardiac damage is as yet uncertain, some authors report good improvement, even in decompensated cases, while others have reported little or no change on the heart condition. It is of utmost importance to determine whether or not valvular deformities can be prevented, but it will require years of follow-up study to evaluate this question.

In the past year we have treated 8 cases of acute rheumatic fever at Norrtulls sjukhus with ACTH or cortisone. From this experience we are unable to state the optimal procedure for using these drugs. In healthy children we have found that the dose of ACTH which will produce a significant decrease in the eosinophil count is correlated with the body weight but in different diseases the effective dose may vary greatly for children of the same age and weight. Therefore it seems more important to correlate the dose with the severity of the disease than to base it on weight or age. In all cases

it is important to control the dosage of the drug with observations of the eosinophil counts.

In the treatment of patients we found:

1) Those who were febrile became afebrile.
2) The sedimentation rate very quickly became normal.
3) The serum anti-hyaluronidase (bovine) decreased.
4) The antistreptolysin titres were unaffected.
5) Murmurs disappeared in most cases.
6) Electrocardiographic abnormalities disappeared.

The disappearance of murmurs does not necessarily indicate healing of endocarditis but may in many cases be due to lessering of the cardiac dilatation. In one patient there were changes in the electrocardiogram following the initiation of treatment with ACTH which subsequently disappeared and which may have been due to an induced potassium deficiency. No other adverse effects of treatment were noted.

DISCUSSION

K.-H. KARLÉN, *Sweden*

I would like to present a brief review of the rheumatic fever cases that we have treated with hormone preparations at the Kronprinsessan Lovisa's Children's Hospital.

There are five cases altogether — three boys and two girls — the clinical picture being dominated by cardiac symptoms in four, while the other had joint symptoms only. All cases were treated with Cortone intramuscularly, the dose ranging between 1.5 and 3 mg per kg body weight per day and the duration of treatment between 13 days and four weeks. An improvement occurred in each case, though in the first one it is questionable whether it was due to Cortone, starting as it did 15 days after the institution of treatment and proceeding very slowly. However, the late improvement in two other cases was almost certainly attributable to the Cortone, for a relapse occurred after the treatment had been discontinued. The improvement was manifested in a declining sedimentation rate in all cases, and in most by falling temperature, better general condition, and disappearance of joint symptoms and signs of decompensation. The murmurs became softer or disappeared, though the Ecg showed only an inappreciable improvement or none at all during the treatment itself. No characteristic changes were found in the eosinophil cell count.

Although these cases do not permit of any definite conclusions, they do suggest that Cortone can often be used to good effect. Presumably the dosage should be adjusted to suit each individual case, being based on the degree of severity. It is striking that in those cases in which Cortone had a rapid effect no relapses occurred. Whether an abrupt discontinuance of treatment

Table

No.	Sex	Diagnosis	Therapy	Dose per kg body weight	Duration of treatment	Improvement	Therapeutic effect obtained on	Recurrence	
								Light	Severe
1360/50	♀	Febris rheumatica Main symptom : heart	Cortone	1½ mg	4 weeks	+	Ca 15th day	—	—
12/51	♂	Febris rheumatica Main symptom : heart	Cortone	1½ mg 3 mg	4 weeks 13 days	+ +	Ca 15th day ?	— —	+ +
508/51	♂	Febris rheumatica Main symptom : heart	Cortone	3 mg	4 weeks	+	1st day (Artic. improvement first)	—	—
51/51	♂	Febris rheumatica Main symptom : artic.	Cortone	1½ mg	2 weeks	+	2nd day	—	—
1457/50	♀	Febris rheumatica Main symptom : heart	Cortone	1½ mg	4 weeks	+	Ca 10th day	+	—

No.	Days passed between end of treatment and relapse	During treatment			
		Ecg	Eosinophil cells per mm^3	SR mm	Temp.
1360/50	—	Slight improvem.	40—130	42—14	No change
12/51	3 4	No change No change	80—120 No change	87—31 35—25	No change, 38° — almost normal
508/51	—	No change	140—150	92—9	Ca 38.5° — almost normal
51/51	—	—	40—10	115—20	39° — almost normal
1457/50	11	Slight improvem.	No change	55—28	38° — normal

increases the risk of recurrence may perhaps be shown by those cases in which we are now terminating the Cortone treatment gradually by giving increasingly small doses. It should be mentioned in conclusion that normalization of the electrocardiogram occurs more slowly than the improvement of the symptoms in general.

R. RINVIK, *Norway*

Cortisone is a specially isolated adrenocortical hormone which acts directly on the tissues ACTH is a hormone which stimulates the general function of the adrenal cortex and from there releases various factors — probably in great part hormonal. One of the hormones is Cortisone.

It has recently been shown that Cortisone can produce an impairment of the androgen secretion in congenital hyperplasia of the adrenals. Hence it is open to question whether substitution therapy may not tend to reduce still further an already impaired adrenal function. For this reason perhaps ACTH rather than Cortisone should be used in children when the purpose is to stimulate the adrenal function.

The following two cases lend weight to this view. In an eleven-year-old girl with rheumatic fever and a four-year-old girl with nephrotic syndrome, Cortone had no effect, but both patients responded immediately to treatment with ACTH.

T. SALMI, *Finland*

As yet we in Finland have little experience of ACTH and Cortisone treatment in rheumatic fever. In the few cases we have treated at the Children's Clinic in Turun Yliopisto, the results have been poor, and relapses have occurred. Cardiac complications, especially insufficiency, appear to be an absolute contraindication. For the time being, salicyl is a better agent to use in acute rheumatic infections.

J. VESTERDAL, *Denmark*

At Rigshospitalet, Copenhagen, we have tried ACTH in a few children with polyarthritis and other diseases, and concurrently the urine has been examined with respect to 17-ketosteroids and glucocorticoids at the Hormone Department of the Serum Institute. It has been found that the secretion of 17-ketosteroids in children cannot be used as a criterion of the adrenal reaction to ACTH, since it does not rise appreciably following injection of ACTH.

The secretion of glucocorticoids, on the other hand, shows a pronounced rise after ACTH, and is therefore a good criterion of the adrenal reaction.

We have found that children respond to smaller doses than do adults, though the dose is not proportional to the weight but to the body surface.

On Influence of Epinephrine and ACTH on the Eosinophil Count of Blood in Severe Infantile Gastroenteritis

by

HILKKA TÄHKÄ, *Finland*

Adrenal insufficiency has often been assumed to be present in connection with severe infantile gastroenteritis. However, the changes taking place in the mineral metabolism, for example, do not support this conception. The significance of the adrenocorticotropic hormone and cortisone in the most varied range of diseases and the author's observation that the adrenals in patients who have died of gastroenritis of long duration were unusually small in size, gave rise to the assumption that in these cases there might be a lack either of adrenocorticotropic hormone or of the so-called sugar-hormones of the adrenal cortex.

The matter has been studied by observing the fluctuations in the eosinophil count of gastroenteritic patients at different stages after the administration of epinephrine and ACTH. The observations show that in the acute stage the number of eosinophil cells is often so low that no conclusions can be drawn, while in some others an abnormal reaction is found, the eosinophil count decreases less than 50 %. If the condition of these children improves the reaction returns to normal in a few days. Cases that do not improve rapidly show a continuous abnormal eosinophilic response to epinephrine. These patients, however, usually reveal a normal eosinophilic response to ACTH. In some very severe cases the eosinophil count did not decrease after the administration of epinephrine or ACTH. With improvement in the condition of the infant the eosinophil cells reaction became normal.

It seems, from the results, that insufficiency of the adrenal cortex may be present in gastroenteric cases of long duration, primarily due to defective ACTH incretion.

From the Hospital for Allergic Diseases, Helsingfors, Finland
Head: Dr. Zaida Eriksson-Lihr

The Function of the Suprarenal Cortex in Allergic Diseases

by

ZAIDA ERIKSSON-LIHR, *Finland*

A study of the function of the suprarenal cortex was undertaken in 129 patients suffering from different allergic diseases. 76 of them were children and 53 adults. 85 patients suffered from bronchial asthma, 21 from allergic eczema, 9 had both asthma and eczema and 14 had other allergic diseases, such as hayfever, migraine and urticaria.

For the study of the *mineral-metabolism,* the Robinson-Power-Kepler test was performed in 127 cases (74 children and 53 adults). 14.9 per cent of the children and 13.2 per cent of the adults gave a positive result in the second part of this test, thus showing *an insufficient excretion of the desoxycorticosterons* as it is seen in Addison's disease. Determinations of sodium, potassium and chlorides in 46 patients gave in 20 instances excessive values for potassium and in 35 low sodium values. In 9 severe asthmatics (5 children) both high potassium and low sodium and chloride values were found such as they are seen in Addisonian crisis, but not regularily between the attacks.

The *carbohydrate metabolism* was studied by using the double glucose tolerance test of Staub, the insulin tolerance test and the adrenalin tolerance test. The Staub test, performed on 42 allergics, showed in most cases a good initial rise, indicating a good sugar absorption. In 15 children under 5 years of age, the second part of the Staub test was too high, thus indicating a failure of factors concerned in removing sugar from the blood. This is often seen in normal children of this age.

The insulin tolerance test (0.1 I.U. per kgr bodyweight i. v.) was performed on 87 patients (55 children and 32 adults). In 75 per cent of the cases the bloodsugar curve showed a result resembling more the curve seen in Addison's disease than that of normal persons. The bloodsugar decrease was rapid, the latency period being in many cases less than 3 minutes, and the increase was slow, so

that it often took several hours before it reached it's original value. The reaction of the allergic patients taking this test was remarkable. Many patients showed a preshock with anxiety, weakness and sweating so marked that the test had to be discontinued by giving glucose. In spite of this early glucose some patients developed a severe shock with unconsciousness and convulsions.

The adrenalin tolerance test was performed in 30 cases in order to get a picture of the glycogen content of the tissues. In only 6 cases was the bloodsugar rise within the normal range of 45 to 60 mgr %, in the other cases it showed an average of 25 mgr %.

In order to verify these results of a disturbed sugar metabolism pointing to a deficiency of the sugar hormones of the suprarenal cortex in 10 children and 15 adults suffering from the above mentioned allergic diseases *the excretion of the 11-oxy-corticosteroids* was determined in the 24-hours' urine by the method of Heard, Sobel and Venning. Of the 10 children, only one showed a normal value. This was a 14 years old girl suffering from bronchial asthma and who had just finished her treatment with ACTH. Of the 15 adults examined, 4 gave normal values.

Blood eosinophilia and lymphocytosis are considered as signs of hypofunction of the suprarenal cortex and are often observed in Addison's disease. In a study of the white blood count in 220 cases of different allergies in children and adults not having persistent signs of infection, a consistent tendency to lymphocytosis and, as is well known, to eosinophilia was observed.

The excretion of 17-ketosteroids in the 24-hour urine was measured in 52 allergic cases using the Zimmerman-Callow method. In only 14 cases were differences from the normal found, compared with values determined by Hamburger for healthy Danish people aged 2 to 102 years.

A comparison of results of the *Thorn test* performed with epinephrine, cortisone (Merck) and ACTH (Organon and Armour) is reported.

These investigations on the function of the suprarenal cortex in allergic states show, by the methods used, a deficiency in the excretion of the hormones of the suprarenal cortex. The greatest percentage of cases showed a deficiency of the 11-oxy-corticosteroids. In a much smaller percentage a deficiency in the desoxycorticosteroids and 17-ketosteroids was found.

REFERENCES

Eriksson-Lihr, Zaida, Per Forssell, Ossi Pettay and Irene Rusk: Investigations of the function of the Suprarenal Cortex in Allergic Diseases. Acta Allergol. 2/4 1949.

—„— L'action de la glande cortico-surrenale dans les états allergiques et le traitement par ACTH. Premier Congres Européen d'Allergie, Paris 1950. Acta Allergol. 3/4 1951.

—„— The function of the suprarenal Cortex in Allergic States and Treatment with ACTH. Proceedings of the Sixth Internat. Congress of Ped. Zürich. 1950 Acta Ped.

DISCUSSION

JENS UGLAND, *Norway*

One of the disease in which etiologic significance has been ascribed to the adrenal cortex is celiac disease. Whether the hypofunction of the adrenal cortex is primary or secondary has not yet been established. In view of the present discussion on ACTH and Cortisone, it may be of interest to mention that Dr. Wennewold and myself have commenced to treat celiac disease with ACTH and with Cortisone at the Department of Pediatrics, Rikshospitalet, Oslo. — The follow-up time is to short as yet to permit any definite conclusions, but the preliminary results are so encouraging that we feel justified in continuing the trials. We have found a remarkably rapid improvement in the general condition. The patients have been in better spirits; they have developed big appetites and rapidly put on weight, and concurrently the stools have assumed a more normal appearance, with a much lower fat content. Further, we have observed an increase in the serum proteins where these have been reduced, a pronounced rise in the serum iron and ascorbic acid, and an increase of the hemoglobin, with normalization of the color index. — In two patients edema and ascites supervened, so that the intake of fluids should be restricted and the treatment combined with diuretics, though not any containing mercury since they increase the secretion of potassium in the tubules. — By this means we could readily check the tendency to edema. We found a good effect with respect to the eosinophil count; slight hypochloremia at the outset, with a rise in the alkali reserve, but no change in the serum potassium values.

In our opinion the drug is useful in that it brings the patient rapidly through a bad period, and by shortening these bad periods it is possible to curtail the course of the disease. — The first patient whom we began to treat with Cortisone has now been without treatment for three weeks, and the condition has so far been entirely satisfactory.

C. E. RÄIHÄ, *Finland*

Evaluation of the effect of ACTH and Cortisone is exceedingly complicated. The eosinophils are considered to be one of the best criteria. In a recent number of Science it is reported that a large dose of ascorbic acid will convert a fall into a rise. Dr. Tähkä has some experience of this.

H. TÄHKÄ, *Finland*

In connection with Professor Räihä's remarks I would like to point out that I have investigated the effect of ascorbic acid in large doses on Thorn's eosinophil reaction in healthy infants. Only 10 cases have been investigated so far, and the results vary considerably. It can be said, however, that large doses of ascorbic acid do seem to affect in some degree the normal course of this reaction. — On the other hand no correlation has been demonstrated between the ascorbic acid content in the plasma of diarrhea patients and the eosinophil cell count or the course of Thorn's test.

B. HELLSTRÖM, *Sweden*

Evaluation of a Thorn test — i. e., the fall in the eosinophil count after ACTH — is difficult in the individual case. First and foremost we must reckon with spontaneous variations in the eosinophil count. According to some authors, major fluctuations occur from one minute to another, but these variations might at least be partly attributable to technical errors. Yet it is certain that quite substantial fluctuations occur in the course of hours, and in part follow the daily rythm. In a series of newborn and two-month-old healthy infants which I investigated together with Drs. Bergstrand and Jonsson, the eosinophil count was found to vary considerably both upward and downward — in one or two cases more than 50 per cent — during the four hours which a Thorn test takes. Thus we may find a spontaneous fall of over 50 per cent, which might be misinterpreted as the effect of ACTH. Earlier investigations have shown these spontaneous variations to be quite large in other age groups, comprising older children and adults.

Another question is whether children may be expected to react in the same way as adults with respect to the degree of the fall in the eosinophil count after ACTH. Thorn tests on the infants, investigated here, show that with a dose per kg body weight corresponding to 25,50 and 100 mg in adults there will be a statistically significant fall in the eosinophil count; but it will average only 30—40 per cent, which is well below the arbitrary conventional limit of 50 per cent.

We have also embarked on an investigation of older children, who appear to react in about the same degree: major individual variations, many with only a very slight fall, although they show not the slightest clinical sign of adrenal insufficiency.

Possibly a fall of 50 per cent or more could be obtained in all cases by increasing the dose further, but it is not certain that these doses would make it easier to differentiate healthy adrenals from those with insufficiency.

L. SALOMONSEN, *Norway*

The possibility of a connection between ACTH-Cortisone and celiac disease is of course merely a hypothesis, but it is an interesting one. An argument against it may be the incontrovertible fact that the incidence of celiac disease rose increasingly in Finland, Denmark and Norway during the war, whereas no such rise was observed in Sweden. But an explanation might perhaps be

that the anxiety, tension and stress associated with war conditions may give rise to endocrinic disharmony, and hence that celiac disease too could be regarded as a psychosomatic disorder.

J. VESTERDAL, *Denmark*

We have investigated the effect of large doses of ascorbic acid, having administered 5 Gm daily for periods of five days during the course of ACTH treatment. No clinical effect whatsoever was found. There was no change in the excretion of 17-ketosteroids in the urine. That of glucocorticoids did not rise further, but rather showed a slight fall, perhaps because a substance like Cortisone unites with ascorbic acid in the adrenals.

Preliminary Investigations of in Vitro Leucocytolysis in Allergy

by

O. PETTAY, *Finland*

Squire and Lee reported in 1947 that in pollen sensitivity the specific pollen added to the patients blood in vitro caused a break down of the white blood cells.

In searching for a more accurate method in standardisation of allergen extracts Berkowitz and Scherago used this principle. They sensitized guinea pigs to dust and examined the degree of in vitro leucocytolysis caused by dust extratcs of varying concentrations. The break down percentage of the white blood cells varied from 20—50 %.

We have examined in this way about 250 patients suffering from different allergic disorders. We have estimated the in vitro leucocytolysis caused by different allergen extracts. In all more than 2 000 tests have been performed. As a rule the results have correlated well with the given anamnestic data, but there are some cases who gave strong skin reactions but where no lysis occured.

Preliminary investigations of drug and tuberculin sensitivities have failed to yield reactions.

Among the more than 300 tests performed on 30 normal persons 3 slightly positive reactions occured.

Further investigations on both the practical and theoretical aspects are in progress.

From the Pediatric Department, Ullevål Hospital, Oslo

Precocious puberty — granulosa-cell tumor

by

ROALD RINVIK, *Norway*

The various causes of pubertas præcox are briefly reviewed, and the case of a 4 year old girl with the disturbance is discussed.

In addition to the secondary sex manifestations she had an abdominal tumor associated with an acute development of ascites. This symptom as well as the presence of multiple enlarged mesenteric lymph nodes, observed at the operation, was considered suggestive evidence of malignancy. The weight of the removed tumor was 1 000 Gm. It had a lobulated, partly cystic appearance and showed a highly polymorphic microscopic picture. The removed lymph nodes were histologically normal. The urinary oestrogenic hormones were increased, and the 17-ketosteroids were higher than normal (13 mg per liter as against 2 to 3 mg per liter, normal for that age). The increased 17-ketosteroid level was considered a reaction from the adrenal gland, provoked by the increased oestrogen content in the blood. Follow-up examination showed normal hormone titers at 3 and 12 months, after the operation.

The signs of puberty disappeared within 6 months, and no evidence of malignancy could be demonstrated one year after the operation.

DISCUSSION

Y. ÅKERRÉN, *Sweden*

A case is described of tumor of the adrenal cortex with female pseudohermaphrodism which was observed at Gothenburg Children's Hospital. At the age of about one year the patient, a girl, had a distinct growth of pubic hair. A careful examination was made, but the excretion of 17-ketosteroids in the urine showed nothing abnormal. The so-called constitutional form of pubertas præcox was therefore diagnosed. Subsequently the patient developed a typical picture of female pseudohermaphrodism with pronounced masculinization (masculine hair distribution, macroclitoris, deep voice, etc.). The symptoms now definitely pointed to an adrenal disorder. Further study of the 17-ketosteroids showed an increased content together with an abnormal steroid which presented a divergent color reaction. Laparotomy then disclosed a tumor about the size of a thumb tip in the adrenal cortex on the right side.

Histologically it had a carcinomatous structure. Its removal did not result in a complete remission of the masculinization. At present — about three years after the operation — there are no signs of a recurrence. — One of the conclusions in this case is that adrenal involvement cannot be ruled out even if the 17-ketosteroids show normal values.

An investigation on the absorption and excretion of radio-iodine in a material of healthy and diseased children

by

H. Hagelsteen and O. Skaug, *Norway*

The clinical diagnosis of hypothyroidism in infants and small children may be very difficult. However, such diagnosis may be of decisive importance to the future of the child. All diagnostic measures must be taken into use, therefore.

In the present investigation the authors have endeavoured to determine the normal absorption of radioiodine in the thyroid gland of children. In previous materials dealing with children the same normal values have been calculated with as in adults.

In this investigation the authors have endeavoured to apply a dosage of radioiodine corresponding to the weight of the child, on the basis of the usual tracer dose of 100 microcuries in an individual weighing 80 kilos.

The counting has been carried out over the neck in a manner to ensure easy reproduction of the geometrical conditions from one individual to another. A simple technique has been introduced for collection and extraction of the isotope from the urine.

The material is partly a normal material, partly a material of patients with thyroid disorders, and comprises children ranging in age from one month to 15 years.

DISCUSSION

M. d'AVIGNON, *Sweden*

The method used by Dr. Hagelsteen, when he dilutes in five liters of water the urine collected in cellulose paper diapers, probably results in major sources of error. Measurement of the radioactivity is done on 0.2 ml of this amount, and if a source of error exists here the error will be magnified twenty-five thousand-fold. According to A. Egmach the radioactivity can be directly

measured in the whole amount of urine, thus obviating these sources of error. In view of the major anatomical variations in the neck and the insignificant amount of activity given, we at Norrtull Hospital have not done any counting over the neck in order to evaluate pathologic deviations. Our evaluations have been on the basis of the urine samples. With the existing facilities the collection of urine involves no major difficulties. One must be certain, of course, that no disturbance of the renal function is present — this by urinanalysis (Heller's test and sediment) and concentration tests. Dr. Hagelsteen found no significant differences between normal cases and hypothyroidism cases on testing combined urine samples taken during 48 hours. Nor, as Skanse has shown, can any such difference be expected. It is the second day's excretion of I^{131} that is increased in hypothyroidism cases compared with normals.

From the Pediatric Department, Ullevål Hospital, Oslo
Head: R. Rinvik, M.D.

Acrodynia caused by exposure to mercury

by

BJARNE ANDERSEN, *Norway*

Only 6 cases of acrodynia have previously been reported in Norway. The author reports 3 additional cases, from various hospitals.

One of these cases, a 20 month old girl, was hospitalized in the Pediatric Department of Ullevål Hospital. Exposure to mercury was suspected as a cause of the disease in this case. There was no history of medication with mercury compounds. It was found out, however, that a gilding and silver plating factory using mercuric chloride for their work was operating in the same building as the patient's home. Her father used to work at the place during spare hours, and her 6 years old brother often played there.

Cutaneous hypersensitiviness to mercuric chloride could not be demonstrated.

The patient was successfully treated with 2.5 mg of BAL every six hours for four days followed by 2.5 mg twice the day for 10 days.

Quantitative determinations of the urinary secretion of mercury gave the following results:

Fourteen days prior to treatment	368	μg	of	Hg	in	each	1 000 ml
When treatment was started	550	„	„	„	„	„	1 000 „
During treatment	2 520	„	„	„	„	„	1 000 „
One month after treatment	85	„	„	„	„	„	1 000 „

Eight of the 9 cases were contacted. A history of *definite* exposure to mercury was obtained in 4 of these cases, and *possible* exposure in 2 cases, while no such relationship was evident from the history in the remaining 2 cases. Quantitative determinations of the urinary secretion of mercury were performed only in the case reported.

Hyaluronidase as an agent facilitating intramuscular urography in children

by

Erik Jacobsson and Herman Gladnikoff, *Sweden*

The use of hyaluronidase has been steadily increasing in many fields of medicine in the past few years, particularly as an agent to facilitate infusions. A method recommended by Olsson and Lövgren, for accelerating, with the aid of hyaluronidase, the absorption rate of contrast medium administered intramuscularly, has been further extended by the writers and has during the past year been almost the only method used at the Samariten Children's Hospital for urographic examinations on infants and young children.

The technique is briefly the following: One ampoule of "hyalase", containing 2.5 VRU (viscosity-reducing units), i. e. roughly 0.005 mg of hyaluronidase, is dissolved in ½—1 ml of a ½ per cent solution of xylocaine and injected into a gluteal muscle. The needle is left in position and after 3—5 minutes the same amount of contrast medium as is used in intravenous urography is injected without further dilution, through the needle. The roentgen examination is then carried out in the customary manner. Through the addition of xylocaine the tissues into which the contrast medium is later to be injected are prepared in advance, so that the injection

causes practically no discomfort. The "hyalase" helps to reduce the resistance of the tissues to the injection of contrast medium, and the spread and absorption of the medium, and consequently the excretion is also thus considerably accelerated. Using this technique, excellent urograms, fully comparable with those obtained with the intravenous method, were made.

The method has been tried out in clinical practice during the past year and has proved to be a valuable aid in the examination of kidneys and urinary passages, particularly in infants and young children.

The Skeletal Age in Diabetic Children

by

C. A. Hernberg and P.-E. Heikel, *Finland*

The skeletal age has been assessed roentgenologically in 81 children (35 girls and 46 boys) with diabetes mellitus, their ages ranging from 15 months to 15 years. Some acceleration was observed in 16 per cent, retardation in 20 per cent and normal conditions ($\pm$ 1 year) in 64 per cent.

In the majority of the cases the retardation seemed to occure in connection with acidosis. In the carliest childhood the retardation perhaps was due to some endocrinal factors subsequent to hepatomegaly. The cause of acceleration was not found, but the relationship between the acceleration and some endocrinal factors in diabetic children stated by other authors is discussed. No definite relationship was revealed between the deviation in the skeletal age and the duration of the disease.

GENERAL MEETING OF THE NORTHERN PEDIATRIC ASSOCIATION

on June 16th, 1951

An acount of the financial status of the association was given by the former Secretary General, Dr. PAUL DRUCKER, Denmark.

After the retirement of Dr. PAUL DRUCKER, Denmark, Professor V. RANTASALO, Finland, Dr. L. STOLTENBERG, Norway, and Professor C. GYLLENSWÄRD, Sweden, the following new board were elected:

Denmark:

Professor P. PLUM
Professor OLUF ANDERSEN
Dr. A. ROTHE-MEYER
Dr. E. W. FLENSBORG, substitute

Finland:

Professor C. E. RÄIHÄ
Professor T. SALMI
Docent P. HEINIÖ
Docent N. HALLMAN, substitute

Norway:

Professor L. SALOMONSEN
Dr. A. NJÅ
Professor A. SUNDAL
Dr. R. RINVIK, substitute

Sweden:

Professor A. WALLGREN
Professor S. SIWE
Docent J. STRÖM, secretary
Professor B. VAHLQUIST, substitute

Revisors: Drs. B. BROMAN, Sweden, and O. MARVEL, Norway, with the substitutes Drs. S. LAHDENSUU, Finland, and E. GJØRUP, Denmark.

At the motion made by the board, the general meeting decided that the next congress was to take place in Oslo in June 1954. Professor L. SALOMONSEN was elected president of the next congress.

Before the President, Professor A. WALLGREN, closed the congress, it was voted to make Professor I. THORLING, Uppsala, an honorary member of the association.

TENTH NORTHERN PEDIATRIC CONGRESS

STOCKHOLM 1951

Scientific and Industrial Exhibition
Slöjdgatan 4

The exhibition will be open as follows:

Wednesday, June 13th, 12.00 to 17.30
Thursday, June 14th, 08.30 to 17.30
Friday, June 15th, 08.30 to 17.30
Saturday, June 16th, 08.30 to 17.30

Exhibition Committee:

Nils Malmberg, Chairman. Edgar Mannheimer, John Lind, Petter Karlberg

Technical and organizing arrangements:

AB S:t Eriks-mässan, Lidingövägen 10, Stockholm 26

The Congress Committee wishes to express its warm appreciation to the following individuals and business firms, who by their cooperation and financial support have given help to this congress:

Aga, AB, Stockholm-Lidingö
Alkafol, AB, Stockholm
Astra, AB, Södertälje
Elema, AB, Hagalund-Stockholm
Enequist, Holme & Co., AB, Stockholm
Ferrosan, AB, Malmö
Findus, AB, Sundbyberg
Grave, Rudolph, AB, Stockholm
Holmgren, Gunnar, professor, Stockholm
Holmgren, Israel, professor, Stockholm
Kabi, AB, Stockholm
Kifa, AB, Stockholm
Leo, AB, Hälsingborg
Mivab, Elektromedicinska Apparater, AB, Stockholm
Mjölkcentralen, Stockholm
Nestlé Products Company, Stockholm
Nordiska Bokhandeln, AB, Stockholm
Norstedt & Söner, AB, Stockholm
Pharmacia, AB, Uppsala
Philips Svenska AB, Stockholm
Sirius, Konservfabriken, AB, Göteborg
Stille-Werner, AB, Stockholm
Svenska Mjölkprodukter, AB, Stockholm
Sängfabriken, AB, Stockholm
Tillquist, Hugo, Ingenjörsfirma, Stockholm
Waller, Erik, med. dr, Stockholm
Vinkelcentrifug, AB, Stockholm
Vitrum, AB, Stockholm
Zeiss, Svenska AB, Stockholm

The Exhibition Committee also wishes to thank dr J. C. Peterson, Nashville, Tenn., U.S.A. for his kind willingness to revise the translations in English.

SCIENTIFIC EXHIBITION

Held in Room A (1—38), Passage E (39—47), Passage F (48—53) and in Room D (54—56)

Room A

		Summaries Page
I:1	**To the Memory of Nils Rosén von Rosenstein**	145
I:2	**Late Vascular Complications in Juvenile Diabetes Mellitus Treated with Free Diet** Lichtenstein, A. †, Larsson, Y., and Ploman, K. G. Stockholm	145
I:3	**Studies of Diabetes Mellitus. — With Special Reference to Late Complications, Liver Function and Diet. — A Preliminary Report** Engleson, Gunnar, Lund	146
II:4	**Electrophoretic Studies of Blood Serum from Rabbits** Lingen, Christian, Stockholm	147
II:5	**Investigations on Serum Amylase in Children** Andersen, Henning, Copenhagen	147
II:6	**A New Type of Bottle for Collecting Urine from Infants** Kaijser, Kurt, Eskilstuna	148
II:7	**A Case of Gargoylism** Jelke, Hugo, Gävle	151
III:8	**The Technique of Oxygen Treatment in Childhood** Larsson, Yngve, Stockholm	152
III:9	**Retrolental Fibroplasia in Sweden** Bjelkhagen, Ingemar, and Lindblad, Yngvar, Stockholm	153
III:10	**The Frequency of Congenital Toxoplasmosis in Gothenburg** Holmdahl, Svante, Gothenburg	153
III:11	**Cerebral Complications Following Acute Respiratory Diseases** Nilsby, Ivar, Lund	153
IV:12	**Studies of the Renal Excretion of P^{32}** Ström, L., Stockholm	154
IV:13	**Studies of Tubercle Bacilli Calmette Vaccine, labelled with Radioactive Phosphorus** Ström, L., and Widström, G., Stockholm	154
IV:14	**Studies of the Dissemination of the Tubercle Bacilli after Intracutaneous Injection of Calmette Vaccine in Humans** Ström, L., Stockholm	158

IV:15 **Radioactive Iodine (I^{131}) in the Diagnosis of Hypothyroidism in Infants and Children**
d'Avignon, M., Stockholm 158

IV:16 **Roentgenologic Examination of the Suprarenal Glands**
Fagerberg, S., Uppsala 159

V:17 **Effects of Ammonium Chloride Acidosis on the Action of Insulin in Dogs**
Mackler, B., Lichtenstein, H., and Guest, George M., Cincinnati, Ohio, U.S.A. 159

V:18 **Duration of Immunity following Vaccination against Diphtheria**
Ericsson, H., and Hesselvik, L., Stockholm-Uppsala 160

V:19 **Presentation of Some Clinical Cases from the Pediatric Department, University Hospital, Uppsala**
Vahlquist, Bo, and co-workers, Uppsala 163

V:20 **The Influence of Infectious Diseases on the Ironbinding Capacity of Serum in Children**
Hagberg, Bengt, Uppsala 163

VI:21 **Technique for Oxygen Therapy in Neonatal Asphyxia**
Åkerrén, Y., and Fürstenberg, N., Gothenburg 163

VI:22 **Changes in Electroencephalograms of Patients with Hypocalcemia due to Hypoparathyroidism**
Hansted, Chr., Copenhagen 164

VI:23 **When and Where do Girls Acquire their Knowledge of Sex**
Auken, Kirsten, Copenhagen 165

VI:24 **The Serum Content of Fe after Injections of Diphtheria Antitoxin**
Räihä, C.-E., and Turunen, S., Helsinki 166

VII:25 **An Attempt to Combat Infant Mortality, and in Particular Early Mortality in Gothenburg**
Åkerrén, Y., Gothenburg 169

VII:26 **Some Principles of Treatment and the Results obtained in the Care of Premature Infants in Gothenburg**
Holmdahl, Kurt, Gothenburg 170

VII:27 **Prematures**
Ahvenainen, E. K., Forsander, O.-A., Louhivuori, A., Malm, E., Niemineva, Kalevi, Rantasalo, Ilari, Räihä, C.-E., and Tallqvist, Hans, Helsinki 171

VIII:28 **Studies on Carbonic Anhydrase in the Blood of Premature Infants**
Berfenstam, R., Uppsala 172

VIII:29 **Fat Absorption Studies in Premature Infants: Influence of Heat Treatment of Milk on Fat Retention**
Söderhjelm, Lars, Uppsala 172

VIII:30 **The Influence of Emotions upon the Electroencephalogram**
Klackenberg, G., Larsson, L.-E., Melin, K.-A., Öhrberg, G., Öhrberg, Kj., and Linder, U., Stockholm 175

VIII:31 **Electroencephalography in Congenital Hypothyroidism**
d'Avignon, M., and Melin, K.-A., Stockholm 175

IX:32 **EEG in Infectious Diseases. — An Electroencephalographic Study of Different Infectious Diseases affecting the Central Nervous System (CNS) made during 1948—1950 at the Hospital for Infectious Diseases in Stockholm**
Holmgren, E. Börje, Stockholm 176

IX:33 **Electroencephalographic Observations in One Hundred Children Suffering from Epileptic Fits**
Frey, T., S:son, and Reinand, T., Gothenburg 176

IX:34 **Neurological and Electroencephalographical Studies of Acute Head Injury**
Larsson, L.-E., Melin, K.-A., Silfverskiöld, B., Öhrberg, G., and Öhrberg, Kj., Stockholm 177

X:35 **The Rhythm of Body Temperature in Children, Studied with Continuous Registration**
Gyllenswärd, Åke, Uppsala 177

X:36 **Megaloblastic Anemia in Children needing Continuous Treatment**
Imerslund, Olga, Oslo 178

X:37 **Unusually Typical Case of Morbus Hand-Schüller-Christian**
Karlén, K.-H., Stockholm 181

X:38 **Electron Microscopic Studies of Tubercle Bacilli**
Enell, H., Lingen, Chr., Melin, K.-A., and Hedman, S., Stockholm 181

Passage E

I:39 **Intravenous Iron Treatment in Children**
Hagberg, Bengt, Uppsala 181

I:40 **The Antibody Situation in Premature Children**
Vahlquist, Bo, Uppsala 182

I:41 **Chloromycetin and Skin Test in Pertussis**
Mossberg, H.-O., Hedlund, P., and Arvidson, M., Stockholm 182

I:42 **Sinusitis in Apparently Well Children**
Bjuggren, G., Kræpelin, E., Lind, J., and Tunevall, G., Stockholm 183

I:43 **BCG Vaccination of Elementary School Children. — A Follow-up Study of Children in Stockholm Elementary Schools**
Enell, Herbert, Stockholm 184

II:44 **Rh-testing and Morbus Hemolyticus Neonatorum. — Experiences of the State Organization for Blood Grouping in Sweden**
Broman, Birger, Stockholm 187

II:45 **Occurrence of Rachitic Signs during Fetal Life in Different Parts of Sweden**
v. Sydow, Gert, Sundsvall, Ranström, Stig, Uppsala, and Berezin, David, Malmö 187

II:46 **Cases of Rickets and Tetany at the Children's Hospital, Gothenburg, 1946—1950**
Nyrin-Brenel, Birgitta, Gothenburg 188

III:47 **Encopresis as a Symptom of Psychic Disturbance**
Höök, Kerstin, Stockholm 189

Passage F

I:48 **Physical Growth during Infancy**
Karlberg, P., and Perman, A., Stockholm 190

I:49 **Total Hemoglobin and Blood Volume in the Newborn Period**
Karlberg, P., Lind, J., and Stahlman, M., Stockholm 190

I:50 **Determination of the Basal Metabolism in Infants, using an Open System**
Karlberg, P., Stockholm 194

II:51 **Some Rare Types of Cardiac and Vascular Malformations**
Mannheimer, E., Bengtsson, E., Krämer, R., Warth, J., Wade, G., Wegelius, C., and Winberg, J., Stockholm 194

II:52 **Congenital Stenosis of the Pulmonary Artery with Septal Defect, but without Overriding Aorta. — Its Diagnosis, Differential Diagnosis and Treatment**
Krämer, R., Stockholm 195

III:53 **Child Welfare Work in Sweden**
Ström, Justus, Stockholm 199

Room D

D:54 **Extended Application of Angiocardiography as an Examination Method**
Lind, J., and Wegelius, C., Stockholm 199

D:55 **Ileus in the Newborn**
Ehrenpreis, Th., Stockholm 200

D:56 **Osteomyelitis in Children. — A Follow-up Study**
Andersson, Å., and Sandegård, E., Stockholm 200

WIFUG

LABORATORY-CENTRIFUGES

FOR ALL SPEEDS AND CAPACITIES ARE NOW WORKING
IN LABORATORIES AND HOSPITALS

In more than 50 countries all over the world

AKTIEBOLAGET WINKELCENTRIFUG

NORRTULLSGATAN 23 STOCKHOLM 6

KIFA

has the honour to invite the members of the Congress to visit our exhibition in the same building as the Congress Bureau where we are showing

For the physicians

Surgical instruments

Hypodermic needles

Blood pressure meters

Apparatus for determination
of Basal Metabolism in infants etc etc

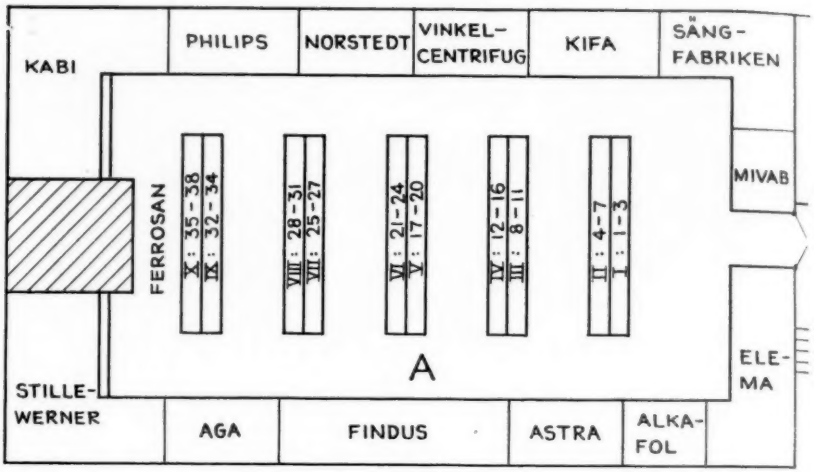
For the Social Workers

Equipment for the nurseries

Please visit also our show rooms at our Head Office

KIRURGISKA INSTRUMENT FABRIKS AKTIEBOLAGET KIFA

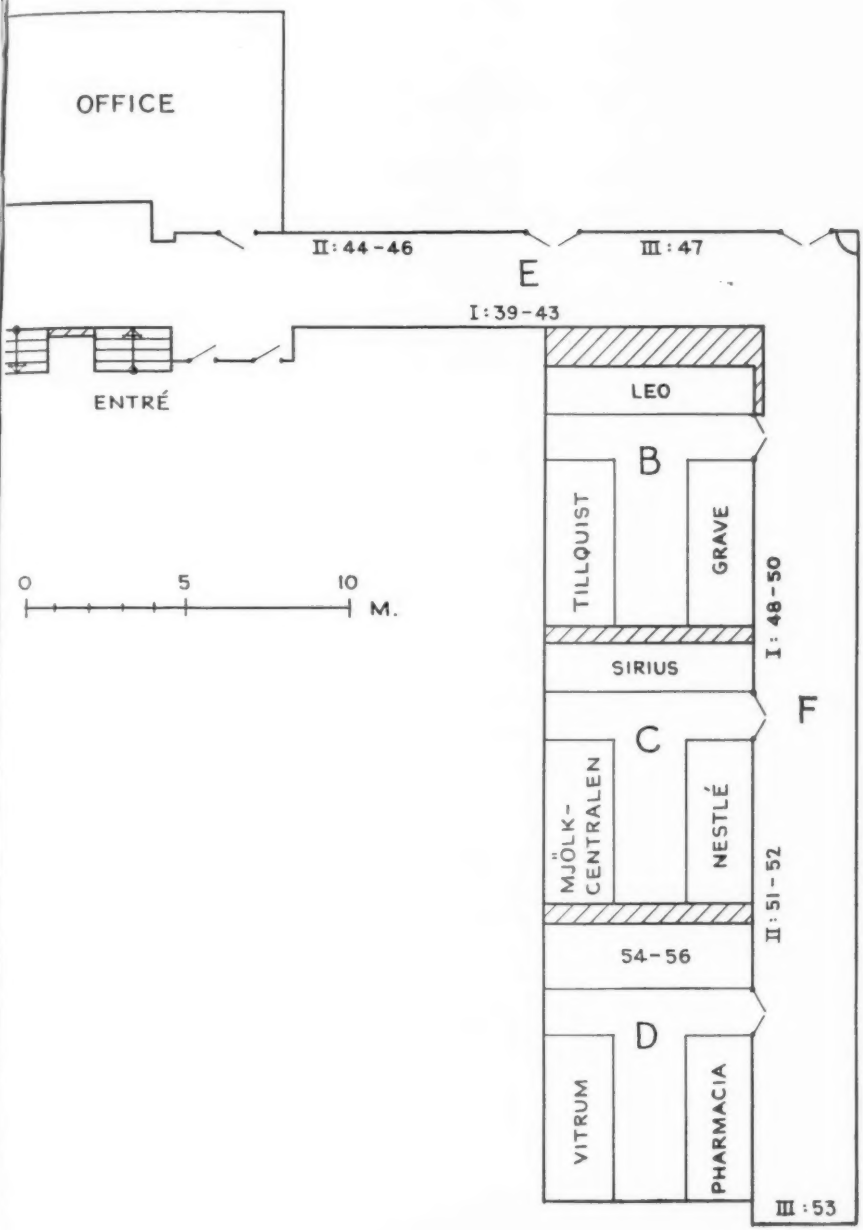
REGERINGSGATAN 31 — STOCKHOLM — TEL. 22 22 60 (växel)



SCIENTIFIC AND INDUSTRIAL EXHIBITION - SLÖJDGATAN 4

TENTH NORTHERN PEDIATRIC CONGRESS

STOCKHOLM, JUNE 1951


OFFICE
II: 44-46
E
III: 47
I: 39-43
ENTRÉ
LEO
B
TILLQUIST
GRAVE
I: 48-50
SIRIUS
F
C
MJÖLK-CENTRALEN
NESTLÉ
II: 51-52
54-56
D
VITRUM
PHARMACIA
III: 53
0
5
10
M.

Aktiebolaget Nordiska Bokhandeln

Drottninggatan 7—9, Stockholm

Det stora lager medicinska nyheter vi ständigt föra har i generationer uppskattats av svenska läkare. Våra i medicinsk litteratur väl kunniga medhjälpare står till disposition med upplysningar om priser och leveranstider för beställningar.

Vår pappersavdelning står till tjänst med utförande av trycksaker, alla slag av blanketter och reservoarpennor.

Aktiebolaget Nordiska Bokhandeln

Postadr. Stockholm 1, Telefon: 23 84 00

INDUSTRIAL EXHIBITION

Held in Room A, Room B, Room C and Room D

Room A

(From the left)

Elema AB
Stockholm-Hagalund, Industrivägen 23. Tel. 27 26 30
Exhibition: Kungsgatan 34, Stockholm. Tel. 21 40 44, 21 40 43

Electromedical apparatus

Advertisement see page 143

Alkafol AB
Stockholm 9. Tel. 45 34 00

Plasticsheeting and Children-articles of plasticsheeting

Astra AB
Södertälje, Strängnäsvägen 22. Tel. 329 80

Pharmaceutical Products

Advertisement see page 144

Findus AB
Sundbyberg. Tel. Sthlm 28 28 40

Findus is the leading preserved foods factory in Sweden. Production covers baby foods, frozen foods, canned and bottled fruits and vegetables, jam and marmalade, fruit juices, soups, mayonnaise, etc. *Findus Baby Foods* are made under supervision of Swedish pediatricians and are regularly analysed by Statens Institut för Folkhälsan (The Swedish Institut of Public Health)

Advertisement see page 149

Svenska AB Gasaccumulator
Lidingö. Tel. 65 25 20

Incubator - Spiropulmator - Oxynator

Advertisement see page 150

Stille Werner AB
Stockholm 4. Bondegatan 21. Tel. 44 92 00

Therapic Apparatus - Diagnostic Instruments - Surgical Instruments

Advertisement see page 155

Ferrosan AB
Malmö. Celsiusgatan 35. Tel. 726 50

Three designs by Thaning used in the company's advertising campaigns

Advertisement see page 156

Kabi AB
Stockholm. Nordenflychtsvägen 53. Tel. 54 09 60

Pharmaceutical Products

Advertisement see page 161

Svenska AB Philips
Stockholm. Gävlegatan 16. Tel. 34 05 80

X-ray Apparatus and Equipment for electromedicine as per following:

X-ray Apparatus Practix - Gordon Armstrong Baby Incubator - Ultra-violet-ray Lamp *Biosol* - Infrared Lamp *Infraphil* - Portable Short-wave Apparatus *Oscilloflux 200* - *Coreco* Colour Camera for Medical Photographing

Advertisement see page 162

P. A. Norstedt & Söner AB
Stockholm. Bryggargatan 17. Tel. 23 29 70

Scientific Laboratory Apparatus

Vinkelcentrifug AB
Stockholm. Norrtullsgatan 23. Tel. 31 38 33

Laboratory Centrifuges

Advertisement see page 135

Kirurgiska Instrument Fabriks AB Kifa
Stockholm. Regeringsgatan 31. Tel. 22 22 60

General Surgical Instruments - Apparatus for Determination of Basal Metabolism in Infants - Baby Articles

Advertisement see page 135

Sängfabriken AB
Stockholm. Norrlandsgatan 16. Tel. 23 17 95
Children's Hospital Beds - Cribs for children 1 to 4 years
Advertisement see page 167

Mivab AB
Stockholm. Luntmakargatan 12. Tel. 10 47 72, 20 70 66
Electro-Medic. Apparatus
Advertisement see page 168

Room B

Rudolph Grave AB
Stockholm. Malmskillnadsgatan 48 C. Tel. 23 37 80
Laboratory Apparatus
Advertisement see page 173

Ingeniörsfirma Hugo Tillquist
Stockholm 7. Nybrokajen 7. Tel. 23 49 55
Instruments for Clinical and Research Laboratories
Advertisement see page 174

Leo AB
Hälsingborg. Tel. 206 00
Pharmaceutical Products
Advertisement see page 179

Room C

Nestlé, Vevey, Suisse
Repr. Disp. L. D. de la Cour. Stockholm C., N. Smedjegatan 13
Tel. 21 61 63
Arobon "poudre" et Nestargel (vendus au Danemark, en Norvège et en Suède) - Lait en poudre Nestlé et Soldor (vendu au Danemark) - Farine Lactée Nestlé et Elédon "jaune" (vendu au Danemark et en Norvège)
Advertisement see page 180

Mjölkcentralen
Stockholm. Dalagatan 3. Tel. 22 60 60
Vitaminized Milk

Advertisement see page 185

Sirius Canning Co
Gothenburg. Byfogdevägen 11. Tel. 19 21 30
Baby Food

Advertisement see page 186

Room D

Pharmacia AB
Uppsala. Tel. 399 40
Pharmaceutical Products

Advertisement see page 191

Vitrum AB
Stockholm. Torsgatan 4. Tel. 22 07 00
The use of an Amino acid preparation (Aminosol)

Advertisement see page 192

SUMMARIES

Room A

A I: 1

To the Memory of Nils Rosén von Rosenstein

Nils Rosén von Rosenstein, 1706—1773, played an important rôle in the development of pediatrics, not only in Sweden but also in many other European countries, through his famous work "Underrättelse om Barnsjukdomar och deras botemedel" (Information about Diseases of Children and their Cure). This Book — according to Ruhräh, the best of its kind previous to 1800 — was translated into Danish, Dutch, English, French, German (6 editions), Hungarian and Italian and was used in several countries as a textbook for more than half a century. von Rosenstein has also been called "the Father of Pediatrics".

The commemorative exhibition comprises:

1. Portrait of Nils Rosén von Rosenstein, painted by Lorens Pasch, sen. Owner: Professor Israel Holmgren, Stockholm.
2. von Rosenstein's own copy of his above-mentioned work. Binding from the eighteenth century.
   Owner: Professor Gunnar Holmgren, Stockholm.
3. Some medals in memory of von Rosenstein.
   Owner: Professor Gunnar Holmgren, Stockholm.
4. Copies of the translated editions.
   Owner: Med. Dr. Erik Waller, Stockholm.

A I: 2

Late Vascular Complications in Juvenile Diabetes Mellitus Treated with Free Diet

Lichtenstein, A. †, Larsson, Y., and Ploman, K. G. Pediatric Clinic at Kronprinsessan Lovisas Children's Hospital

The late degenerative vascular complications are at present the most serious problem in clinical diabetic research. The authors, in their series of 257 cases of juvenile diabetes, have compared the mortality and frequency of complications of these cases, allowed an unrestricted diet with those of other similar series, treated with diet. The mortality was low — 6.9 %. Vascular disease, coma and infections constituted the chief causes of death.

The age at onset of diabetes varied fairly evenly between 2 and 12 years of age. The duration of the disease was as follows:

66 patients had had diabetes less than 5 years
75 „ „ „ „ from 5 to 10 years
62 „ „ „ „ „ 10 „ 15 „
44 „ „ „ „ more than 15 „

The symptomatology of diabetic retinopathy is described. It is subdivided into three stages. Stage I is characterized by microaneurysm and hemorrhage, stage II by the appearance of exudate. In stage III there is proliferation of the connective tissue in the retina (retinitis proliferans) and rapid deterioration of the vision. The frequency of retinopathy increased with the duration of diabetes and after 15 years of the disease it was 72.7 %. In the whole series it was 33.2 %. Retinopathy of stage III, however, occurred in only 12.1 % of the cases with 15 years of duration and in 4.8 % in the whole series.

Diabetic nephropathy — intercapillary glomerulosclerosis as described by Kimmelstiel and Wilson — is not easily recognized during lifetime. Constant albuminuria was the first sign of kidney damage and it was present in 15.6 %.

Advanced peripheral arteriosclerosis with calcification could be diagnosed with the means of X-ray in 7.9 %. There was hypercholesterolemia in 25 % and a rise in blood pressure in 26 % of all cases.

The etiology of the vascular complications in diabetes is still unknown. The frequency of vascular disease was not higher in this material treated with free diet than in other diet-treated series. The complications seem to set in to about the same extent regardless of whether the patients have been treated with or without special diet. Since free diet offers diabetic children a chance to lead a virtually normal life it is superior to special diet treatment.

A I: 3

Studies of Diabetes Mellitus. With Special Reference to Late Complications, Liver Function and Diet. A Preliminary Report

Engleson, Gunnar. Pediatric Clinic, University of Lund

Since 1949, studies have been carried out on certain problems concerning diabetes mellitus including both children and adults treated with "free diet".

These investigations have been made in order to obtain the frequency of late complications, particularly the vascular-renal type, and the relationship between diabetes mellitus and liver function, with special attention to lipid metabolism, and particularly the occurrence of dysfunction of other endocrine organs.

The investigations are still in progress and only preliminary results are available.

In a number of diabetic patients with outstanding vascular-renal lesions, including several cases of Kimmelstiel-Wilson syndrome, treatment with choline has been tried and in some cases favourable results have been achieved.

The results so far obtained in the above mentioned investigations are presented in tabular form.

A II: 4

Electrophoretic Studies of Blood Serum from Rabbits

Lingen, Christian. Pediatric Clinic at Kronprinsessan Lovisas Children's Hospital, Stockholm

To further investigate the immunology of tuberculosis, comparative studies with electrophoresis, according to the method of Antweiler, were done on blood serum from rabbits before and after Calmette-vaccination, and also before and after infection with tuberculosis. The effect of streptomycin on blood serum from rabbits infected with tuberculosis was studied with the same method.

The investigations were done in the following manner. Every series of rabbits (about 5 rabbits) was studied with electrophoresis every day during one week under normal conditions. Thereafter, every rabbit was either Calmette-vaccinated (0.1 ml intraderm.) or injected with tubercle bacilli i. v. (bovinus) and followed with electrophoresis every second day, with duplicate tests. Differential blood counts were done daily in order to follow the changes in the lymphocytes.

A II: 5

Investigations on Serum Amylase in Children

Andersen, Henning. Dronning Louises Children's Hospital, Copenhagen

The increasing understanding of the rôle, played by disturbances in the digestion of starch, in certain dyspepias in infancy, especially shown by Dorothy H. Andersen in her exellent work on celiac disease, is the basis of the present work.

A microestimation of serum amylase is described, based upon the method of Nørby. By increasing the digestion time to 12—24 hours, one determination can be made with only 25—50 mm^3 serum, derived from capillary blood. The error of the method is equivalent to Nørbys method.

With the method, 95 normal children of all ages, most of them being within the twelve first months, have been examined. From a very low level at birth, the serum amylase values increase during the first half year, and from then on fall within Nørbys limits for normal adults. No difference could be found in the values from girls and boys.

Serum amylase as a function of body weight shows the same curve, both being an expression of age.

The variation in the serum amylase level during the day is very little. The low serum amylase values in the first months of life is in accordance with similar low pancreas amylase values found by C. Dueholm & H. Andersen in a previous work on duodenal fluid.

Finally some preliminary results of serum amylase estimations on children with various forms of dyspepsias are shown.

A II: 6

A New Type of Bottle for Collecting Urine from Infants

Kaijser, Kurt. Children's Department of the General Hospital, Eskilstuna

Many different kinds of urine bottles for infants have been suggested. I have in mind a urine collecting vessel that is simple to use without having any complicated arrangements, and yet is a good collector of urine. Some sorts of difficulties thereby are to be overcome.

Fig. 1.
Top row: Urine-bottles for girls.
Bottom row: Urine-bottles for boys.

1. In the first place, it is necessary to design different bottles for boys and girls.

2. Secondly, one must endeavour to achieve a proper fit for the bottle. The rapid growth of the child and the consequential change in proportion in the genital and perineal tracts, necessitates the use of several different sizes of bottle, even during the first year of life. It seems to me desirable to have bottles which would be suitable for the following ages: premature, new-born, 3-months, 6-months, 9-months, 1 year and round about 1½ years.

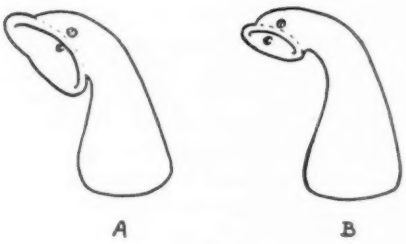


Fig. 2.
A. *Urine-bottle for a girl.*
B. *Urine-bottle for a boy.*

If one has access to these different sizes of urine bottles, one can choose a bottle appropriate for the child regardless of the child's age.

3. If the neck of the bottle is made fairly flat, so that it will lie comfortably between the child's thighs, the opening can be fixed over the penis or vulva and remain secure and undisturbed without the child continually kicking against the bottle.

4. To attain the necessary volume the storage part of the bottle is fashioned to lie beneath the thighs.

In the case of boys it is unnecessary to use any fastening other than a gauze bandage from a hole on either side of the bottle. The bandage is carried around to the back where it is crossed, brought around to the abdomen and tied. In the case of girls, one may fasten the bottle with additional security by means of adhesive tape from the bottom of the bottle to the gluteal region.

The urine bottles, which are made of strong pyrex glass, have been worked out in conjunction with Messrs. Rudolph Grave, AB, Stockholm, Sweden.

Fig. 3.
The Urine-bottle in position.

A II: 7

A Case of Gargoylism

Jelke, Hugo. Westergren Children's Hospital, Gävle

The patient, a boy, was born 31/3 1943 as the only child of healthy parents. Inquiry into the family history disclosed no antecedent cases. The birth weight and length were within normal limits. The child, who had hare-

lip and cleft palate, developed slowly, both mentally and physically. The first teeth did not erupt until he was 14 months old, and he did not begin to walk until he was 20 months old. At 9 months of age, a lumbar kyphosis was observed. The head increased rather rapidly between the age of 2 and 4 years, but the linear growth was very slow in this period.

In 1949 he was observed at the Children's Hospital, Gävle, for *gargoylism*, organic heart disease and an umbilical hernia. He then weighed 16.7 kg and was 93 cm tall. Most striking was the almost negroid appearance of the face: a saddle nose with a flat tip, a large mouth with protuberant thich lips, bushy eyebrows and thick brushlike hair. In the middle of the forehead was a visible and palpable vertical ridge. The limbs were short, the hands stubby and clawlike.

There was a kyphosis in the upper lumbar region. A systolic murmur was audible over the entire heart. The blood pressure was 140/70. A large umbilical hernia was present. The abdomen was fairly large. Both the liver and the spleen were palpable about 3 cm below the thorax. The corneæ were generally cloudy due to a dense deposition of small opaque spots, masking the fundi.

The plasma lipoids were 958 mg/100 ml of which 225 mg/100 ml were cholesterol. A glucose tolerance test had an abnormally flat and low curve, which rose in 1 hour from 80 to 114 mg/100 ml, where it persisted for about one hour and a half.

Roentgen examination of the skeleton revealed a considerably retarded ossification corresponding to an age of about 2 years and 8 months. The skull was large and the sella turcica elongated. Lumbar kyphosis with angulation at the level of the first and second lumbar vertebra was seen. These vertebral bodies were deformed and showed a small incisure in the anterior border. The lower ribs were broad with a slender rudimentary neck portion. The shaft bones were short and thick, as were the metacarpal and metatarsal bones and the phalanges, which were of spongy structure.

Intelligence quotient according to the method of Terman & Merrill was 63.

Therefore this is a classical case of gargoylism presenting all the main symptoms in a striking manner.

A III: 8

The Technique of Oxygen Treatment in Childhood

Larsson, Yngve. Pediatric Clinic at Kronprinsessan Lovisas Children's Hospital, Stockholm

The different methods of oxygen administration now in use at the Pediatric Clinic of the Kronprinsessan Lovisas Children's Hospital in Stockholm, are described.

A III: 9

Retrolental Fibroplasia in Sweden

Bjelkhagen, Ingemar, and Lindblad, Yngvar. Samariten Children's Hospital, Stockholm

There are 38 known cases of retrolental fibroplasia in Sweden, none occured before 1945. A map has been prepared showing their distribution. The details of the study will appear later in Acta Pædiatrica.

A III: 10

The Frequency of Congenital Toxoplasmosis in Gothenburg

Holmdahl, Svante. Children's Hospital, Medical Department and Sahlgren's Hospital Departments, Gothenburg

Antibodies against toxoplasma, tested by neutralizing test and dye test, have been found in about 50 per cent of pregnant women, with a high titre, indicating active toxoplasmosis in 3—5 per cent. The investigation has not been able to show statistically an increased frequency of neutralizing antibodies among women whose children died perinatally, premature deliveries, or abortions.

During a 3-year period, in about 18 000 deliveries, only a single case of infantile toxoplasmosis has been diagnosed clinically. Even in systematical post-mortem examinations in all stillbirths and neonatal deaths no case of toxoplasmosis has been found.

Congenital toxoplasmosis consequently seems to be a very rare disease in this city. A single serologic test cannot be used to prove the diagnosis of toxoplasmosis in an individual case. The presence of antibodies possess a clinical value only if an actually arising titre can be demonstrated.

Literature:
Holmdahl, S.: Toxoplasmos och graviditet, Göteborg 1949 (Swedish with an English summary).

A III: 11

Cerebral Complications Following Acute Respiratory Diseases

Nilsby, Ivar. Pediatric Clinic, University of Lund

Cerebral complications following acute respiratory diseases have been observed in 76 children treated in the Pediatric clinic of Lund during the ten year period of 1940—1950. Seventy per cent of the cases occurred in infants. Forty-nine of the 76 children were boys, 27 girls.

Usually, neurologic symptoms followed the acute infection after an interval of 6—7 days. Common symptoms were: convulsions, stupor or coma, rigidity, paresis, irritability, dizziness, personality changes, vascular and metabolic disturbances. Fifty per cent of the patients were afebrile at the onset of neurologic symptoms.

Examination of the spinal fluid usually showed a moderate mononuclear pleocytosis with a slight increase of the protein content. In a few cases, no

abnormality was demonstrable. Bacteriologic examinations were always negative.

The duration of the neurologic symptoms was short, frequently less than a week, Fifty-one patients (67 per cent) had no symptoms when discharged. Four patients (5 per cent) died and 21 (28 per cent) had residual symptoms.

In one case, microscopic examination of the brain showed no abnormality. Edema and congestion were found in two cases; the microscopic examination showed cellular infiltration of the meninges and of the walls of the veins in the white matter. The fourth case showed only cellular infiltration of the meninges.

A follow-up study with the aim to get information of prognostic value has just been started.

A IV: 12

Studies of the Renal Excretion of P^{32}

Ström, L. Pediatric Clinic at Norrtull Hospital, Stockholm

The renal excretion of P^{32} was studied in a total of 106 individuals, 101 infants and children and 5 adults (28 normals, including the 5 adults, 15 prematures and 63 pathological cases).

After an intravenous injection, P^{32} can be found after about 5 minutes in the urine. The excretion of P^{32} increases in the course of the first hour to considerable amounts as compared to the activity of the blood, and after about 20 minutes the specific activity is higher in the urine than in the blood.

In individuals with renal disease the pattern of the excretion of P^{32}, invariably digresses from that of normals. From a statistical comparison between the groups of normal and diseased individuals we were able to establish that the values for the specific activity of the urine in the pathological group were always lower than the corresponding specific activity of the blood. However, simultaneously with the disappearance of the clinical symptoms of the renal disease, the values of the specific activity of urine rose to a normal level and exceeded those for the specific activity of blood.

Also in the cases of prematures there is a decreased excretion of P^{32} corresponding to the very low phosphate clearance.

A IV: 13

Studies of Tubercle Bacilli Calmette Vaccine, labelled with Radioactive Phosphorus

Ström, L., and Widström, G. Pediatric Clinic at Norrtull Hospital, Stockholm

In order to determine the time in which the tubercle bacilli reach various organs in experimentally infected guinea pigs, and the channels by which the bacilli were disseminated, the following investigation has been carried out at Norrtull's Hospital in Stockholm.

Radioactive phosphorus was added to Dubos' fluid medium, which was then inoculated with various strains of tubercle bacilli. After a lapse of about 10 days, the bacilli were separated from the radioactive medium by centrifugation, and thoroughly washed. Guinea pigs were inoculated subcutaneously with a suspension of the labelled bacilli and were killed after varying intervals. The amount of activity per gram of tissue was determined for the different organs. The result of the investigation appears in Table 1.

Table 1

Guinea pigs	Bacterial strain	Hours after i. m injection	Activity per gram tissue								Act/cc	
			Lymph gland	Spleen	Lung	Kidney	Liver	Heart	Muscle	Marrow	Blood	Urine
1	Jamaica	48	815	47	90.9	108.7	35	—	—	—	—	—
2	H. 37	48	735	41.6	132	26	66	—	—	—	—	—
3	,,	24	687	34.8	—	—	45.8	—	—	—	—	—
4	,,	48	—	24	61	—	44.6	—	—	—	—	—
5	,,	96	261	32	25.6	—	54.6	—	—	—	—	—
6	,,	168	244	19.2	23.6	—	92.8	—	—	—	—	—
7	BCG	54	100	39.5	54	31.4	70	—	—	—	95	110
8	,,	45	400	76	—	48	18	—	—	—	60	60
9	,,	54	—	56	40	42.5	39	—	—	—	85	90
10	,,	54	349	86	55	85	13	—	—	—	115	120
11	Ravenel	12	8800	400	132	67	—	280	—	7500	720	802
12	,,	16	4800	600	210	75	—	—	80	6000	110	113
13	,,	24	5500	315	144	94	—	—	—	—	60	80
14	,,	4	2000	480	156	81	76	150	40	—	60	68
15	,,	4	1640	350	—	100	85	170	52	8000	34	40
16	,,	5	1600	250	88	80	59	140	132	—	66	80
17	,,	5	2200	350	126	60	110	72	150	3600	88	100

Four other groups of guinea pigs have been examined. In the 1st, the animals were inoculated with tubercle bacilli 8 weeks previously, in the 2nd with tubercle bacilli 2 weeks previously, in the 3rd with BCG 3 weeks previously and the 4th group were the control animals. All the animals were injected intravenously with a radioactive Calmette-vaccine. The amount of activity used was 1.25 million impulses (of β rays) per minute.

The animals were killed after 12 and 24 hours. The Table 2 shows the dissemination of the organism. There was some difference in the dissemination, when the bacilli were injected intracutaneously and subcutaneously. Most of the vaccine seems to be taken up by the liver and spleen and not by the lymph nodes. A priori, we would have expected that most of it would be caught in the lungs, as this is the first filter of the intravenous channel. In the immunized animals there seems to be an extremely rapid elimination of activity. In the controls, the equilibrium between the activity of the blood and the urine is reached very soon. This elimination of activity might be a sign or even an expression of the degree of immunity.

Table 2. Guinea pigs injected with radioactive Calmette-vaccine

Guinea pigs	Bacterial strain	Hours after i. v. injection	Activity per gram tissue						Act/cc	
			Lymph gland	Spleen	Lung	Kidney	Liver	Bone Marrow	Blood	Urine
1	K3 8 Weeks	12	690	4045	2360	1120	2130	3260	530	960
2	" "	12	1380	9350	2310	934	2460	2500	410	—
3	" "	24	1200	5040	1640	910	2520	2960	314	2140
4	" "	24	925	4090	1380	1840	3780	1400	340	1140
5	K3 2 Weeks	12	930	2780	1890	1520	4170	1000	370	860
6	" "	24	650	4720	—	1000	3040	1625	890	530
7	BCG 3 Weeks	12	1360	1980	1980	—	3600	2500	380	860
8	" "	12	—	4200	2830	510	2450	1960	410	—
9	" "	12	1680	2560	2230	—	4750	3120	245	520
10	" "	12	1860	2000	—	960	4160	2980	360	585
11	" "	24	980	2300	—	1050	2170	710	312	1000
12	" "	24	—	3100	890	1200	2260	970	360	—
13	" "	24	1000	3820	930	500	3750	—	385	1170
14	" "	24	1120	1500	610	370	4970	1050	410	1190
15	Control	12	1545	6660	930	1175	1990	6260	550	375
16	"	12	1328	5350	2220	865	3820	3760	460	420
17	"	24	12700	1390	2500	1465	3720	3460	350	—
18	"	24	14200	3520	874	804	2780	4000	340	400

A IV: 14

Studies of the Dissemination of the Tubercle Bacilli after Intracutaneous Injection of Calmette Vaccine in Humans

Ström, L. Pediatric Clinic at Norrtull Hospital, Stockholm

If labelled tubercle bacilli are injected intracutaneously into an individual already immunized with BCG, there seems to be a retention of the labelled vaccine at the site of injection. In these individuals it takes considerably longer to find measurable radioactivity in the lymph glands and the activity disappears very slowly from the site of injection. This retention seems to correspond to the Koch's phenomenon.

A IV: 15

Radioactive Iodine (I^{131}) in the Diagnosis of Hypothyroidism in Infants and Children

d'Avignon. M. Pediatric Clinic at Norrtull Hospital, Stockholm

A IV: 16

Roentgenologic Examination of the Suprarenal Glands

Fagerberg, S. Department of Roentgenology,
University Hospital, Uppsala

Roentgenological examination of the suprarenal glands might be used to show anatomical changes of the suprarenal glands.

The previously used perirenal insufflation of gas is considered dangerous and is technically too difficult to gain widespread popularity. A great advantage was the introduction of the method of Rivas in 1948, which utilizes the insufflation of oxygen presacrally. This gives an interstitial emphysema of the retroperitoneal space around the kidneys and the suprarenal glands, and between them. The suprarenal glands are surrounded by contrasting gas and are visible on roentgenograms. The technique is simple and the method probably whithout risks.

This examination is possible to use also in children, with the following technique:

1. The patient is prepared as before urography.
2. Half an hour prior to the examination suitable basic narcotic is administered rectally, on the ward.
3. Immediately before the injection deeper ether narcosis is administered.
4. The child is placed in prone position with the abdomen on a pillow.
5. The injection is performed in the midline between anus and coccyx with a small lumbar puncture needle. The needle is inserted 2—4 cm (according to size and age of the patient) with the point in the loose presacral tissues.
6. After aspiration, the needle is connected to a Forlanini apparatus and oxygen is injected. If the needle is in correct position this will meet only little resistance.
7. According to the size of the child, 250—600 ml of oxygen is introduced.
8. For one hour after the injection, the patient is kept in supine position with elevated chest and head in order to facilitate the propagation of the gas upwards. Then the pictures are taken.

Only a few examinations have been performed in children — the youngest four months of age — and about ten in adults.

X-ray pictures will be shown in the exhibition.

A V: 17

Effects of Ammonium Chloride Acidosis on the Action of Insulin in Dogs

Mackler, Bruce, Lichtenstein, Henrik, and Guest, George M. Children's Hospital Research Foundation and the Department of Pediatrics, University of Cincinnati. Cincinnati, Ohio, U.S.A.

There exists much evidence that in patients treated for diabetic coma the action of insulin is inhibited by conditions of ketonemic acidosis. Reasons for the apparently decreased effectiveness of insulin under such conditions

are by no means well understood. During the evolution of a diabetic crisis the development of varying degrees of insulin resistence may be reasonably ascribed to a number of mutually aggravating factors. Some investigators have assumed that the state of acidosis per se inhibits the action of insulin, but positive evidence on this point is scanty. The experiments here reported were devised as a means of studying how the effects of insulin might be altered in severe ammonium chloride acidosis in normal animals, a type of acidosis that could be investigated apart from the other factors involved in the ketonemic acidosis of diabetic subjects.

To determine the effects of a non-ketogenic type of acidosis on the action of insulin, insulin sensitivity tests were done on six non-diabetic fasted dogs in normal states and in states of severe acidosis, induced by slow intravenous perfusion of ammonium chloride.

During the development of acidosis in the fasted animals the blood sugar tended to rise slightly, with maximal increases around 35 mg per 100 cc above the fasting level. Standard doses of insulin administered intravenously in severely acidotic dogs produced less fall in the concentration of blood-sugar, with slower rate of fall and slower recovery to initial levels in the three hour test period, than in the same dogs in non-acidotic states. Levels of plasma-potassium and inorganic phosphorus tended to change very little or to remain stationary, after injections of insulin in the acidotic dogs; whereas in non-acidotic states changes in concentration of plasma-potassium and inorganic phosphorus (both sharply decreasing and then returning to initial levels) paralleled closely the changes of blood-sugar induced by insulin.

Conclusion: Conditions of acidosis probably inhibit the action of insulin by interfering with processes of phosphorylation that are involved in the cellular uptake of sugar, potassium and phosphorus from the plasma.

The continuous intravenous perfusion apparatus will be shown on a photograph and the results will be demonstrated on several charts.

A V: 18

Duration of Immunity following Vaccination against Diphtheria

Ericsson H., and Hesselvik L. State Bacteriological Laboratory, Stockholm, and Pediatric Clinic, University Hospital, Uppsala

The essential principle for immunization against diphtheria, during the prevailing epidemiological situation in Sweden, is based on the assumption that a basic immunity lasting at least five years may be produced by two single doses of purified, adsorbed diphtheria toxoid. The basic immunity thus established does not grant any permanent reliable protection, but a "booster" dose should raise the titer of antitoxin above the protective level in a very short time, if a greater immunity should be required by a change in the epidemiological situation.

The correctness of this assumption has been tested in 31 school-children. Eighteen of these had been given only one dose for basic immunization, the

rest had been given two doses with one year's interval. Five years later only two cases in each group showed a level of antitoxin exceeding 0.1 unit per ml. Ten days after the "booster" dose, however, all the children showed titers exceeding 0.5 units per ml.

A V: 19

Presentation of Some Clinical Cases from the Pediatric Department, University Hospital, Uppsala

B. Vahlquist and co-workers, Uppsala

1. Heterosexual precocity in a male infant due to percutaneous absorption of oestron.
2. Hyperparathyroidism in a boy 12 years old.
3. Icterus gravis in an Rh negative child due to sensitization against factor c.
4. Spontaneous healing of presacral adenosarcoma in an infant.

A V: 20

The Influence of Infectious Diseases on the Ironbinding Capacity of Serum in Children

Hagberg, Bengt. Department of Pediatrics, University Hospital, Uppsala

Recent investigations with isotope iron have demonstrated a definite impairment of erythrocyte formation during infections, especially in children. The development of the anemia in cases of severe infections is often very rapid, indicating probable hæmolytic mechanisms. Whether changes in the total blood volume occur or not, is still obscure. Certainly, pronounced alterations in the metabolism of iron are inherent. The present author has studied the relation between the duration of infection and the depression of the ironbinding capacity in serum. In sharp contrast to the steep and often pronounced decline of serum iron during the first few days of a severe bacterial infection (pneumonia, meningitis etc.), the ironbinding capacity exhibits a slow but steady decline over a period of many days. In chronic infections, the depression of the ironbinding capacity of serum is often relatively more pronounced than the depression of the serum iron.

The serum iron determinations were made by the method of Vahlquist, adopted for serum quantities of 0.3—0.5 ml. The ironbinding capacity of serum was analyzed with the spectrophotometric method of Rath-Finch (J. of Clin. Investig. XXVIII: 79—85, 1949).

A VI: 21

Technique for Oxygen Therapy in Neonatal Asphyxia

Åkerrén, Y., and Fürstenberg, N. Children's Hospital Medical Department, and Sahlgren's Hospital, Maternity Department I, Gothenburg

The first principle in the treatment of asphyxia is to supply oxygen as quickly and effectively as possible. In cases of apnea and defective infla-

tion and air-content in the pulmonary alveoli (possibly complicated by aspiration into the bronchioli and pulmonary parenchyma) ordinary methods of supplying oxygen to the respiratory tract are ineffective or useless.

In Gothenburg a technique has been tried-out of supplying oxygen to the gastro-intestinal tract. A double catheter is passed down into the stomach, one tube supplies oxygen; the other serves as a safety-valve to prevent too great a dilatation of the stomach. The gas spreads rapidly, as appears from X-ray examinations, as a rule within about 15 seconds, to the greater part of the small intestine. When supplied for a longer period, the passage of gas from the anus can often be observed, showing that the colon also contains oxygen. In this way a large oxygen-gas deposit is established from which oxygen can be absorbed. Anoxemia is thereby counteracted and the respiratory center may be able to regain its excitability.

If and when this succeeds, respiratory movements appear or are improved. When this occurs the greatest possible oxygen content in the air inhaled is desirable. In order to obtain this the stomach catheter system is used in combination with a funnel-shaped mask. Through the tube of the funnel is drawn a catheter, the free end of which is directed towards the childs upper lip and placed about 1—1.5 cm away from it. Oxygen is blown with high speed through the catheter. In this way is achieved on the one hand an increase in the oxygen content of the air inspired, and on the other hand a stimulation of the skin in order to overcome the depression of the respiratory centre. With a two-way valve oxygen from the same oxygen tube can be passed alternately through the stomach catheter or the mask.

In mild cases of asphyxia treatment with the mask may be used from the beginning.

Literature:
Åkerrén, Y., & Fürstenberg, N.: Journ. Obstetr. & Gynecolog. Brit. Emp. *57*: 705, 1950.
—„— Svenska Läkartidningen 1950 *47*: 1501 (nr 26).
Barcroft, J.: Researches on Pre-Natal Life, Blackwell, Oxford, 1946.

A VI: 22

Changes in Electroencephalograms of Patients with Hypocalcemia due to Hypoparathyroidism

Hansted, Chr. Dronning Louises Children's Hospital, Copenhagen

Summary: Odoriz and co-workers have demonstrated alterations in electroencephalograms in patients with hypoparathyroidism. This statement has been confirmed in two cases examined before and after treatment. The predominant changes are the appearance of solitary or long runs of slow potentials of increased amplitude. These variations disappear or decrease considerably, when normal Ca content in blood serum has been established.

A VI: 23

When and Where do Girls Acquire their Knowledge of Sex

Auken, Kirsten, Copenhagen

Three hundred and eight women aged 20 to 36 years, admitted to 6 different hospitals about in Denmark, were asked the age at which they knew about sexual conditions, more particularly about coitus.

The average age for knowledge of coitus was 14.4 years.

295 women were also asked the source of their knowledge. None refused to answer the questions.

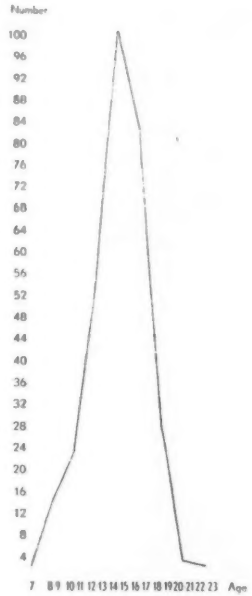


Fig. 1. Age at knowledge of coitus.

Main source:

46.1 % said that friends were the main source of their knowledge of coitus
11.9 % „ „ the mother was „ „ „ „ „ „ „ „

Of those with their original knowledge from friends 39.3 % had felt the want of guidance, while this was the case with only 5.9 % of those who had acquired their knowledge, from their mothers, as appears from Table 1.

Main source plus secondary source:

Many women had their knowledge from two or more sources. The 295 women had their total sexual knowledge from 503 different sources, including main and secondary sources:

Table 1

Main source	Number	per cent	Country	Town	City	Capital	Age at knowledge of coitus	Felt want of guidance %	Partially felt want of guidance %	Did not feel want of guidance %
Friends	136	46.1	42	16	39	39	14.2	35.3	11.7	58.9
Mother	35	11.9	10	4	12	9	14.2	5.9	5.9	88.2
Fiancé	25	8.5	11	0	5	9	17.8	52.0	12.0	36.0
Animal life	26	8.8	23	0	2	1	12.2	15.4	15.4	69.2
Sister	25	8.5	13	2	5	5	13.6	32.0	12.0	56.0
School	9	3.1	1	0	1	7	14.4	11.1	0	88.9
Books	15	5.1	4	1	6	4	15.4	20.0	6.7	73.3
"Colored" booklets	5	1.7	1	0	1	3	16.4	80.0	20.0	0
Other sources	10	6.5	7	3	4	5	14.4	42.1	10.5	47.4
Total	295	100	112	26	75	82	14.4	31.0	10.9	58.2

Table II

64.7 % gave friends as main or secondary source
25.1 % „ life among animals „ „ „ „ „
18.6 % „ the mother „ „ „ „ „
15.9 % „ the fiancé „ „ „ „ „
12.5 % „ sisters „ „ „ „ „
11.5 % „ school „ „ „ „ „
11.5 % „ books „ „ „ „ „
4.5 % „ so-called "colored" booklets as main or secondary source
6.4 % „ other sources

Thus, we may be justified in concluding that the 295 girls of the present series had acquired their knowledge of sexual questions chiefly from friends, and only to a smaller extent from their next of kin.

A VI: 24

The Serum Content of Fe after Injections of Diphtheria Antitoxin

Räihä, C.-E., and Turunen, S. Pediatric Clinic, Helsinki

It was reported, during the WHO metabolic congress held in March 1950 in Stockholm, that peroxidase is associated with the metabolic phenomena affecting the neutralization of the diphtheria toxins. Such reports are also found in the literature (Agner, 1950). No answer was known to the question put forward by Räihä as to the reaction of serum iron to injections of diphtheria antitoxins. As a consequence, we have studied the phenomenon

and found that the first injection produces a slight rise in the iron content after 2—3 weeks, the second injection results at first in a slight fall, followed in about 2 weeks by an abrupt rise which persists for only a few days.

*

An Oxygen Incubator by Santasalo-Sohlberg AB, Helsingfors, is shown.

A VII: 25

An Attempt to Combat Infant Mortality, and in Particular Early Mortality in Gothenburg

Åkerrén, Y. Children's Hospital, Medical Department, Gothenburg

At the Northern Pediatric Congress in Helsingfors in 1946 figures concerning infant mortality in Gothenburg, during the 5-year period 1941—45 were reported. It was evident that a certain stagnation had occurred in the tendency toward improvement. This was due to a halt in progress — indeed a tendency to worsening — in the early mortality figures (deaths during the first 7 days after birth).

In consequence I have attempted to draw up and to carry out in practice a program for combating, above all, early mortality. The chief points have been the following: 1) Close co-operation with the obstetricians. A co-operation made easy in Gothenburg by the fact that more than 95 % of all deliveries take place in the two municipal maternity clinics, in which the Children's Hospital doctors are responsible for the pediatric care. Above all, rational care of the new-born infant immediately after birth has been aimed at, in accordance with the formula: the obstetrician should be the pediatrician in the labor-room. Particular attention has been paid to asphyxia treatment (cf. Åkerrén & Fürstenberg). 2) Speedy placing of all new-born babies in need of continued observation or treatment under special pediatric or other care (premature department, other pediatric or even child surgery department). 3) Improved care of the premature infants (cf. K. Holmdahl). 4) Scrupulous and continuous pediatric supervision of all new-born babies, among other things by daily visiting of the new-born babies' ward. 5) Autopsy in all cases of still-birth and early mortality, by which the causes of death, and its pathogenesis, may be established, thus providing a starting-point for improving the efficiency of obstetrical and neonatal care.

The figures for births, infant mortality, early mortality and still-births for the city of Gothenburg during the period 1941—50 are given in the following table.

Literature:
Y. Åkerrén: Proceed. VIIIth North. Pediatr. Congr., 1946, Act. Pæd. *35*:77, 1947.
—„— & N. Fürstenberg: Act. Pæd., present volume.
K. Holmdahl: Act. Pæd., present volume.

Year	Living births	Deaths during first year		Deaths during first week		Still-births	
	N:o	N:o	%	N:o	%	N:o	%
1941—45	27154	750	2.76	445	1.64	569	2.05
1946	6211	131	2.11	82	1.42	110	1.74
47	6466	144	2.23	100	1.55	108	1.64
48[1]	6389	118	1.85	78	1.22	110	1,69
49[1]	6108	116	1.90	82	1.34	93	1.50
50[1]	5773	99	1.71	70	1.21	100	1.70
1946—50	30947	608	1.96	412	1.33	521	1.66

[1] The figures for these years are preliminary.

A VII: 26

Some Principles of Treatment and the Results obtained in the Care of Premature Infants in Gothenburg

Holmdahl, Kurt. Children's Hospital, Medical Department and Sahlgren's Hospital, Maternity Departments, Gothenburg

Since 1948 improved results have been obtained in the care of the premature infants in Gothenburg. The value of oxygen administration is stressed, particularly gastro-intestinal administration. It is important to delay starting the administration of nourishment. It is important to reduce the handling of the infants to minimum. For feeding of all infants with a birth weight of less than 2 000 gm, colostrum has been employed, in some cases complemented with Aminosolglucose. In comparison with breast milk, colostrum with its relatively high protein content should be of value. To evaluate the results of this care, the mortality in three other series of premature infants is compared with the author's series of 677 infants. The basic material in these three series (Crosse 1949, Birmingham, England, 1 141 children, Selander, 1949, Sweden, 544 children and Taylor et al., 1949, Denver, U.S.A. 480 children), is rather similar to the author's own material. An analysis of the mortality in the different weight groups shows a very favorable figure reached in the Gothenburg series in the group between 1 510—2 000 gm. For the groups 1 010—1 500 and 2 010—2 500 gm the mortality was lowest in the series from Denver, which, however, included 15 % negro infants.

Of the 121 premature infants, who died within four weeks after birth, 84.1 % died within the first 48 hours. Of the 19 infants who died after the second day of life, 13 died of brain injuries, deformities or debility. From the distribution of the deaths, with a considerable peak immediately after birth, and from the nature of the causes of death it appears that disturbances of nutrition and infections were seldom the cause of death.

A further reduction of the mortality is thus possible mainly be reducing the mortality in the first 48 hours. An intensified cooperation between obstetricians and pediatricians is necessary here.

A VII: 27

Prematures

Ahvenainen, E. K., Forsander, O.-A., Louhivuori, A., Malm, E., Nieminen, Kalevi., Rantasalo, Ilari., Räihä, C.-E., and Tallqvist, Hans.
Children's Clinic, Helsinki

Of the premature infants delivered at the Women's Clinic of the University of Helsinki over a period of 30 years, one half weighed over 2 kg, and one fourth 1 500—2 000 g.

The premature Infant mortality at the Children's Clinic has decreased from about 60 % to 12 %. The control of infective diseases is the main cause for this fall.

In the weigth group of 1 000—1 500, treatment in incubators with oxygen is essential. In this group, the poor development of the capillaries and the relatively small alveolar volume as compared to the dead space of the respiratory passages increases the difficulty of supplying oxygen to the tissues to such extent, that the basic metabolic rate can be increased by introducing additional oxygen into the air to be breathed.

The anatomic underdevelopment finds its counter-part in enzymatic underdevelopment. Cytochrome c increases in the heart muscle with an increase in weight and age. In the normal newborn, co-carboxylase is considerably more abundant than in mothers, and it decreases with advancing age. As a sign of enzymatic immaturity, the pyruvic acid value of the blood is elevated in prematures even at their birth, and frequently persists on a high level up to 40 years of age. With better management of infectious diseases, the weight curves begin to rise in the second week of treatment.

On the basis of about 300 autopsies performed on premature babies (1946—1950), pneumonia occupies the first place as a cause of death and intracranial hemorrhage comes second. Among pulmonary causes, hyaline membranes are commonnest, in addition to pneumonias. With the decrease of the total mortality, the ratio of intracranial hemorrhage and inflammatory diseases in the autopsy material has remained practically unchanged.

In the early spring of 1949, 15 cases of sepsis due to *Pseudomonas æruginosa* were diagnosed among the newborns at the maternity hospital which is our chief source of supply of premature babies. The blood culture was positive in 9 cases, and in 11 the causative agent of the disease was found in the spinal fluid. Two cases survived. In the autumn of 1949 there was another outbreak of *Pseudomonas æruginosa* sepsis in which several premature infants died. After this period observations were begun on the bacterial content of the water which had been used to wash the premature babies. The percent of sterile washings between December 1949 and March 1951 rose from 20 to 37. For the same period, bacteria of the Pseudomonas group decreased from 21 % to 3 %.

A VIII: 28

Studies on Carbonic Anhydrase in the Blood of Premature Infants

Berfenstam, Ragnar. Department of Pediatrics, University Hospital, Uppsala

Earlier investigations have shown (Stevenson, Berfenstam and others) that the activity of the enzyme carbonic anhydrase — an enzyme, which is necessary for the carbonic acid metabolism — is low in the blood of newborn infants in comparison with the activity in the blood of adults. The activity in the blood of premature infants is still lower.

The author has been able to show that there is a good correlation between the degree of maturity of the infant and the activity of the enzyme. If an infant with a low birth weight is born at term, according to the mothers statement, it is often thought that the mother is wrong: "the baby is prematurely born." The author has investigated some of those cases, and has found that they, despite of their low birth weight, have an enzyme activity corresponding to that of full term infants.

If the infant gets a transfusion of blood from an adult donor, the enzyme activity in the blood of the infant will increase. This increase is a consequence of the addition of the adult red blood corpuscles and an activation by the donors plasma. This is demonstrated by the intravenous and intramuscular injections of plasma — which itself contains *no* enzyme — giving a high increase in the activity of the infants blood. This effect is connected with a factor in plasma which is nonelectrolytic, heat stable and able to pass through a dialysis-membrane.

There is still some discussion whether or not the low activity of the carbonic anhydrase in the blood of the premature infants is of any importance for the respiration and the metabolism. If future studies should indicate that this is the case, we might use this activating factor therapeutically.

A VIII: 29

Fat Absorption Studies in Premature Infants: Influence of Heat Treatment of Milk on Fat Retention

Söderhjelm, Lars. Department of Pediatrics, University Hospital, Uppsala, and the Department of Pediatrics, University of Texas Medical Branch, Galveston, U.S.A.

It is frequently stated that premature infants absorb fat poorly and, in many places, this has led to the employment of low fat milk mixtures for these infants. In order to determine whether any possible effect on fat retention results from the heat treatment of milk, fat balance studies were undertaken wherein breast milk and cow's milk were subjected to different temperatures for variable lengths of time.

About 100 fat balance studies, mostly of 4 to 6 days' duration, were made on more than 30 premature infants. The fat of the diet was supplied

from breast milk, raw, frozen or heated at various temperatures for different intervals of time, or from cow's milk, pasteurized, or subjected to heating at various temperatures for different periods. The nature of the treatment of the milk did not influence the degree of fat retention in these experiments.

A VIII: 30

The Influence of Emotions upon the Electroencephalogram

Klackenberg, G., Larsson, L.-E., Melin, K.-A., Öhrberg, G., Öhrberg, Kj., and Linder, U. Pediatric Clinic at Kronprinsessan Lovisas Children's Hospital

In order to study the importance of emotional influence upon the electroencephalographic record, which is of special importance in EEG-examinations of children, a number of young persons from both sexes have been shown short movies with suddenly appearing shock-effects, under simultaneous recording of the EEG. The results are presented in records and diagrams.

A VIII: 31

Electroencephalography in Congenital Hypothyroidism

d'Avignon, M., and Melin, K.-A. Pediatric Clinic at Norrtull Hospital and at Kronprinsessan Lovisas Children's Hospital

We have, so far, carried out EEG examinations in 42 cases of congenital hypothyroidism. The Terman-Merrill intelligence-test was used to determine the mental development of the patient. In individuals with an intelligence quotient below 45, the EEG showed markedly slow waves or were dysrhythmic in 84 %; while in the other 16 % the waves were only moderately slow or the tracing slightly dysrhythmic, that is, none had normal EEG.

In the group with intelligence quotients of 45—70, 50 % had markedly slow waves or were dysrhythmic and 50 % had moderately slow waves or were slightly dysrhythmic.

It is not until mental development approach the normal state, that the EEG becomes normal. In patients with quotients between 70 and 90 only 22 % showed slow waves or dysrhythmical records. In the group between 90 and 110 there were only 10 % abnormal and in individuals with intelligence quotients above 110 there were none with pathologically slow waves or dysrhythmic EEG:s.

To summarize: 42 cases of followed-up congenital hypothyroidism examined with EEG showed slow waves or dysrhythmic records mainly when mental development was retarded.

A IX: 32

EEG in Infectious Diseases
An Electroencephalographic Study of Different Infectious Diseases affecting the Central Nervous System (CNS) made during 1948—1950 at the Hospital for Infectious Diseases in Stockholm

Holmgren, E. Börje. Hospital for Infectious Diseases, Stockholm

The material consists mainly of cases of:

I. *Viral infections of the CNS*
1. Poliomyelitis and polioencephalitis (with or without paresis).
2. Meningo-encephalitis ac. serous (viral?).
3. Para-and postinfectious meningo-encephalitis (in measles, parotitis, varicella and infectious mononucleosis).

II. *Bacterial infections of the CNS*
1. Tuberculous meningitis.
2. Purulent meningitis (meningococcal, pneumococcal, and due to influenza bacilli).
3. Encephalopathy in pertussis.

III. *Observation of infections of the CNS*
Most of the cases have been examined two or several times with electroencephalography. The exhibition will show the value of EEG as means of making a diagnosis of a CNS-infection, as means of following the course of the cerebral dysfunction objectively, and partly in the recognition of a postencephalitic residue specifically (epilepsy) thus getting prognostic information.

The EEG appears to be very valuable in diagnosis, especially in those cases which have little or no change in the cerebrospinal fluid. In several cases of functional nervous disorders e. g. hysteria, or functional somatic diseases, the method has a great value in excluding a CNS-infection.

The use of EEG has also a very great value as an aid to the clinicians in following the progression or regression of the meningo-encephalitic process, and to show if and when a normal state has returned. In some cases the EEG-investigation has shown a subclinical postencephalopathy rather early, before it could bo shown clinically. This is of great value for the clinician, who has to decide whether or not to give prophylactic anticonvulsive therapy.

Later on the definite result of the study will be published in detail.

A IX: 33

Electroencephalographic Observations in One Hundred Children Suffering from Epileptic Fits

Frey, T. S:son, and Reinand, T. Electroencephalographic Laboratory, Sahlgren Hospital and the Medical Department, Children's Hospital, Gothenburg

The electroencephalographic records of one hundred epileptic children aged two to sixteen years were examined. About two-thirds of the children were between 5 and 13 years of age.

The records were analyzed with regard to alpha frequency, degree of dysrhythmia, presence of "spike and wave" and other episodic phenomena, focal abnormality and marked fast activity. It was found that:

1. Focal abnormality was common, occurring in 66 per cent of the records.
2. Focal abnormality was more often situated in the left hemisphere than in the right. Forty-three per cent of the foci were on the left side and 20 per cent on the right.
3. It was difficult to predict the presence or absence of focal abnormality from the history. The cases with a known external cause did not show focal abnormality more often than the others.
4. The children with aggressive explosive behavior showed more dysrhythmia and episodic phenomena than the others.
5. Spike and wave phenomena were more common in the cases of petit mal than in the ones with convulsions only.

Conclusion

As focal electroencephalographic abnormality is so common in children suffering from epileptic fits, it seems probable that exogenic factors have much to do with the development of their disease.

A IX: 34

Neurological and Electroencephalographical Studies of Acute Head Injury

Larsson, L.-E., Melin, K.-A., Silfverskiöld, B., Öhrberg, G., and Öhrberg, Kj. Pediatric Clinic at Kronprinsessan Lovisas Children's Hospital, Stockholm

In order to continue the studies of the electroencephalogram in acute head injuries and to obtain pretraumatic as well as post traumatic records, neurological and electroencephalographical examinations were done on young boxers before and after their matches. After hard blows against the head a number of cases showed such clinical and electroencephalographical findings, as are usually connected with the diagnosis of brain concussion. Some typical records and their different changes are demonstrated.

A X: 35

The Rhythm of Body Temperature in Children, Studied with Continuous Registration

Gyllenswärd, Åke. Department of Pediatrics, University Hospital, Uppsala

An apparatus consisting of thermocouples coupled to a potentiometer with an automatic writer which registers the temperature every other minute, has made it possible to study the rectal temperature and its dependence on several factors.

Similar researches have been made (Jundell, Gofferjé, Kleitman), but they were all performed with ordinary thermometers, with rather long intervals between the measurements. Also the basal conditions were not ideal, as the children were disturbed during sleep.

The body temperature has a pronounced daily rhythm which varies in different individuals and ages, especially as regards to the amplitude. Such a rhythm is observed in premature babies before they can quite regulate their own temperature. To keep the temperature constant, more warmth is needed during the night than during the day. The extent of wakefulness is not the only factor which decides the body temperature, as these small infants are always asleep between feedings. The distribution of the feedings during the day did not produce any fluctuation worth mentioning.

This investigation shows that the rhythm is endogenous, and is only little influenced by the activity of the muscles of children lying in bed. When a child is sleeping during the day-time, the temperature falls, but not as much as in the night. If the child continues to sleep in the evening, the temperature falls more, even though it had been constant for several hours. If he is awakened, just at this time, the temperature falls, although at other times it rises with awakening.

The temperature rises a little (ca 0.°5 C) when a child is awakened during the night. When he falls asleep at that time when the temperature would normally rise in the morning, the temperature continues to rise, while at other times it falls with going to sleep.

Endogenous factors, which are probably connected with the vegetative balance, thus dominate the rhythm of the temperature.

The rising of the body temperature from meals has been observed only in small infants. The rising then occurs 1—1½ hour after the meal.

Variations in the room-temperature even at 7° C do not, at least in children older than two years, influence the body temperature.

The temperature during fever is as yet incompletely studied, but appears to be influenced by several factors connected with the etiology and the actual treatment.

A X: 36

Megaloblastic Anemia in Children needing Continuous Treatment

Imerslund, Olga. Pediatric University Clinic, Oslo

From a clinical and therapeutical point of view the megaloblastic anemias in children can be divided into 2 main groups:

1. Cases without tendency to relapse, Zuelzer and Ogdens "Megaloblastic Anemia of Infancy". Goats milk anemia.
2. Cases in which the anemia recurs when the treatment is stopped. As in pernicious anemia in adults, continuous treatment is necessary for the maintenance of satisfactory hematopoiesis. The exhibition will contain data and photomicrographs from 9 cases of idiopathic megaloblastic anemia without achlorhydria, belonging to the second group.

A X: 37

Unusually Typical Case of Morbus Hand-Schüller-Christian

Karlén, K.-H. Pediatric Clinic at Kronprinsessan Lovisas Children's Hospital, Stockholm

Demonstration of a case, a 2½ year old boy without any heredity for this disease. Symptoms started in August 1950. All classical symptoms are demonstrable. The diagnosis was verified by puncture of the spleen and of a focal process in the frontal bone.

He has been treated with Cortone since april 5th, 1951.

A X: 38

Electron Microscopic Studies of Tubercle Bacilli

Enell, H., Lingen, Chr., Melin, K.-A., and Hedman, S. King Gustaf V:s Research Institute, Stockholm

The use of electron microscopic technic has made it possible to study more closely the structures in different bacilli, their changes at different ages and their reactions, when influenced by different remedies. Normal tubercle bacilli in Dubos cultures, of different ages, and their changes, when different remedies (streptomycin, para-aminosalicylic acid, conteben and diplomycin) were added to the cultures, have been studied and the results are presented.

Passage E

E I: 39

Intravenous Iron Treatment in Children

Hagberg, Bengt. Department of Pediatrics, University Hospital, Uppsala

Twenty children with anemia, mainly of iron deficiency type, were treated with intravenous injections of saccharated iron (Intrafer, Pharmacia). The diagnosis of iron deficiency was substantiated by low serum iron values and a high iron binding capacity of the serum. The effect of the treatment was evaluated by determinations of hemoglobin, erythrocytes and reticulocytes. In all cases, free from infections, good responses were obtained. A few cases, which had not responded to long periods of oral treatment, improved after intravenous therapy. Evidence was obtained that iron could be administrated, without toxic reactions, in amazingly high dosage. Thus, repeated venipunctures can be avoided, which is especially valuable in pediatric practice.

A schedule is given of its indications in childhood, dosage, and mode of administration. The case material is presented in tables. The response of hemoglobin and reticulocytes as well as the content of iron in serum, following intravenous injections are given in graphs. The results are compared with those obtained in adults, by other authors.

The results of this study permit the following conclusions concerning the use of saccharated iron in pediatric practice:

1. Intravenous iron therapy is a valuable adjunct to oral therapy under certain circumstances.
2. In the majority of cases it has a good and rapidly inaugurated effect.
3. Most children will tolerate comparatively large doses of "Intrafer", 10 mg per kg of body weight.
4. It ought to be stressed finally, that the total amount injected must not exceed the real need, since the body can not easily get rid of the superfluous iron.

E 1: 40

The Antibody Situation in Premature Children

Vahlquist, Bo. Department of Pediatrics, University Hospital, Uppsala

Premature children are very susceptible to infections. This group of diseases rank high among the causes of death. Various factors contribute to this poor resistance against infections. Few of them have been sufficiently analyzed.

Antibodies are transferred from mother to child in utero. Recent studies on antistreptolysin and antistaphylolysin have shown (Vahlquist et al., Lancet 1950: II: 851) that these types of antibodies appear in the blood of the fetus only after the middle of gestation. Prematurely born children have antibodies in concentrations which approximate those of children born at term. The same seems to be true also for diphtheria antitoxin (Dancis, personal communication); only the lowest weight groups have titers materially below those of fullterm children.

The capacity of the premature child to form antibodies has not been investigated to any extent. The response of newborn premature children to a single injection of diphtheria toxoid is not only delayed, as it is in fullterm newborn children, but the final titers achieved also fall much below those of the fullterm children. Several premature children did not show any response at all. Such a slow and unsatisfactory response to antigens may explain the liability of prematures to develop septicemias.

E 1: 41

Chloromycetin and Skin Test in Pertussis

Mossberg, H.-O., Hedlund, P., and Arvidson, M. Hospital for Infectious Diseases, Stockholm

One hundred and fifty children, in-patients at the Hospital for Infectious Diseases in Stockholm, have been studied at various stages of pertussis. One half of the children received chloromycetin orally and the other half received a placebo powder. They were also followed by means of an intracutaneous skin test, agglutinogen test. The reactions have been compared with those of normals.

Hemophilus pertussis could not be found, culturally after the treatment with chloromycetin was finished. The course of the disease was much milder in the cases treated with chloromycetin in the preparoxysmal stage of the disease, while in the paroxysmal stage of the disease, however, there was no effect or — as in babies — only a suggestive effect.

The skin reaction shows a progressive increase during the course of the disease. The skin reaction during treatment with chloromycetin is demonstrated. The test in children without whooping-cough gives an idea of how long the reaction will last.

Further details will be published.

E I: 42

Sinusitis in Apparently Well Children

Bjuggren, G., Kræpelin, S., Lind, J., and Tunevall, G.
Pediatric Clinic at Norrtull Hospital, Stockholm

One hundred and eighty-eight apparently healthy children from 3 to 8 years of age, who were examined during the winter months, showed a notably high incidence of sinusitis.

The diagnosis of sinusitis was based primarily upon positive roentgen findings, which in this study, were graded +, ++ and +++. With a +++ finding the sinus was absolutly obliterated, with ++ it was largely obliterated but there was a small amount of air visible within its borders, and with + there was a definite mucosal thickening.

Roentgen findings	Number of children with positive roentgen findings on one or more examinations during the winter 6 months			
	Home children (69 cases)	Day-home children (76 cases)	School children (43 cases)	Total (188 cases)
+	12	16	10	38
++ and +++	34	34	15	83
Sum of positive roentgen findings	46	50	25	121

83 of 188 children, or 44 %, had at some time or other during the winter, 6 months, definite roentgenologic evidence of sinusitis ++ or +++. Eleven of those cases showed such evidence in each of three examinations. Home children and day-home children were chosen from the same social groups (i. e. age, siblings, home, economic circumstances etc.).

In the majority of cases with high-grade changes (++ and +++) the diagnosis was confirmed by sinus irrigation. In the first stages of examination, irrigation was carried out in essentially all cases with positive roentgen

findings (+, ++ and +++), by which we found, as a rule, that mucopurulent secretion was recovered in those cases showing ++ and +++ roentgen changes. In the second stage, therefore, puncture of the sinuses was done only in the high-grade (++ and +++) cases.

Only in exceptional cases did children show more definite catarrhal symptoms, and in many cases they appeared to be completely free of infection.

In the second stage, 58 sinus irrigations were done in 114 children. Specimens for bacteriological culture were taken with a special technique. Forty-one pure cultures were obtained, among which there were 19 of pneumococci and 12 of hemophilus influenzae.

In cases not showing definitely purulent secretion, no further treatment was carried out, the sinusitis usually clearing up in the interval between examinations.

Consideration was given to the rôle of heredity, the child's own allergic condition and occurrence of eosinophilic cells in the blood and the nasal secretions. Allergy was, however, probably causally related to the sinusitis in only a small number of cases.

E I: 43

BCG Vaccination of Elementary School Children

A Follow-up Study of Children in Stockholm Elementary Schools
Enell, Herbert. Stockholm Elementary School Board and the Pediatric Clinic at Kronprinsessan Lovisas Children's Hospital, Stockholm

Voluntary BCG vaccination of children in the first or second classes of Stockholm elementary schools was introduced in 1945; since then approximately 40 000 children have been vaccinated. A considerable number of those children vaccinated in 1945 or slightly earlier or of those vaccinated during the same period at a dispensary or day-home still attend the elementary schools. A follow-up study made now therefore permits both conception of the duration of the post-vaccinal allergy to tuberculin and of the ability of BCG vaccination to protect against clinically manifest tuberculous infections.

The present follow-up study was started in the spring of 1950 and includes 4 000 children from widely divergent social strata and from five schools. The children were tested with the patch test and the Mantoux reaction to 1 mg. The sensitivity to tuberculin in various classes and ages was first plotted on diagrams, with and without consideration to earlier BCG vaccination.

The number of tuberculin-negative children who had not undergone BCG vaccination amounted to approximately 20 per cent; about half of them had refused vaccination for various reasons. In approximately two-thirds of the new reactors — invertors — the change-over had taken place before they started school; the majority of the remainder became positive during their first years at school. Of the new reactors half of them had shown clinical signs of tuberculous infection. Clinical tuberculosis occurred in only seven

cases after BCG vaccination with a positive reaction. The investigation shows that the overwhelming majority of school children had been BCG vaccinated, and that they remained tuberculin-positive for a long period.

In view of the fact that the BCG vaccinated children comprised three-fourths of the whole material and the controls, *i. e.*, those not vaccinated, only one-fourth, the importance of BCG vaccination and its prophylactic value among school children is considered to be well established. In order to throw more light on the problem, an investigation was made of the living conditions (possible crowding) of the children in the respective groups and of the various social groups. The results are shown in tables and diagrams.

E II: 44

Rh-testing and Morbus Hemolyticus Neonatorum

Experiences of the State Organization for Blood Grouping in Sweden
Broman, Birger. The Rh laboratory, Stockholm

The exhibition shows the organization of Rh-testing in Sweden built up by the Rh laboratory (The State Chemico-Legal laboratory, Rh department), Stockholm.

Blood with a high titre of Rh antibodies is collected from patients all over the country and sent to the Rh laboratory. This blood is then used to prepare Rh testing sera at the laboratory, standard anti Rh (anti D) sera subsequently being sent to the different hospitals as required. Decentralization of Rh testing (mainly with agglutinating sera) is thus made to an increasing extent without importing any sera from abroad.

Some of the results of this work are shown — antenatal Rh-testing, the search for Rh antibodies, the centralized care of Rh immunized pregnant women at an obstetrical department where special arrangements have been made for the mother and child.

Examples are given of the necessity of both clinical and serological investigations to make it possible to give a prognosis for the child in the individual case.

Other examples illustrate the importance of following the suggested practical measures in clinical medicine with regard to the Rh factor.

E II: 45

Occurrence of Rachitic Signs during Fetal Life in Different Parts of Sweden

v. Sydow, Gert, Sundsvall, Ranström, Stig, Uppsala, and
Berezin, David, Malmö

Collection of the material. At the obstetric-gynecological department in Malmö (56° N.), Uppsala (60° N.) and Sundsvall (62° N.) fetuses and infants dying on the day of birth or earlier, during 1949 have been examined for histological signs characteristic of rickets. The collection comprises 111 cases from Malmö, 50 from Uppsala and 69 from Sundsvall. The distribution of different weight groups appears from the table below.

The study material consisted of the anterior parts of the 1st or 2d and the 6th or 7th ribs including the costo-chondral junction.

Method of preparation: Fixation in 10 % formalin. Partial decalcification in Müller's solution. Celloidin embedding. Frozen sections stained with hematoxylin-eosin.

Interpretation. Three alterations were separately searched for, namely, structural irregularities at the costo-chondral junction, hyperplasia and hypertrophy of the cartilage cells at the costo-chondral junction, and the occurrence of osteoid. The structural irregularities at the costo-chondral junction were those typical of rickets, a more or less thorough mixing-up of bone and cartilage with a disappearance of the normally distinct and straight zone of ossification. The hyperplasia and hypertrophy of cartilage cells also showed characteristics typical of rickets. The finding of osteoid was considered positive only in those cases where osteoid was found outside the immediate vicinity of the ossification zone and the periostium (where small or moderate amounts of osteoid were found in almost 100 %).

Results. It appears from the table that signs characteristic of rickets are very common even at an early stage of fetal life. The youngest fetus presenting all the three rachitic signs was one weighing 200 grams and measuring 21 cm in length, delivered in the 5th fetal month by legal abortion. The incidence of osteoid is even higher in the fetuses weighing less than 1 500 gm than in those weighing more than 1 500 gm, the difference being 18.0 ± 6.4 %. No connection was established between the occurrence of rachitic signs and the mother's living conditions during pregnancy, her health, diet, housing, supply of vitamin D, or insolation. And no significant difference was found between the incidence of rachitic signs in the different geographic regions.

									Total
Structural irregularities	+	+	+	—	+	—	—	—	
Hyperplasia-hypertrophy	+	+	—	+	—	+	—	—	
Osteoid	+	—	+	+	—	—	+	—	
— 500	2	—	—	1	—	3	27	28	61
510—1 500	3	2	2	1	—	2	23	19	52
1 510—2 500	—	5	—	6	—	2	14	19	46
2 510—	—	2	—	—	—	4	16	49	71
Total	5	9	2	8	—	11	80	115	230

Distribution of rachitic signs on different weight groups.

E II: 46

Cases of Rickets and Tetany at the Children's Hospital, Gothenburg, 1946—1950

Nyrin-Brenel, Birgitta. Children's Hospital, Medical Department, Gothenburg

Despite many years of preventive child-welfare work, rickets and tetany still occur in Gothenburg. During the past five years, 72 patients from the city, who were so diagnosed, have been admitted to this hospital. Of these,

38 had both tetany and rickets, while 34 had only rickets, 49 boys, 23 girls. The age-distribution was the usual one, with the largest number of cases between the ages of 6 and 9 months. The seasonal distribution was also the usual one with a distinct maximum for cases of tetany during the period January to April.

Only one of the children was prematurely born. Thus premature birth plays practically no pathogenic part in this series, indicating that the prophylactic measures in the prematurely-born have operated satisfactorily. In 32 of the cases, the supply of Vitamin D was insufficient (the dose too small, too short or too irregular). In 24 cases no prophylaxis against rickets had been given at all. In 16 cases satisfactory doses of Vitamin D were said to have been given, but the statements made on this point are probably unreliable. Sixty-nine percent of the patients belonged to the Child Welfare Centre; during the five-year period in question, the average total membership for the city was about 90 %. In only 12 % of the cases exclusive breast feeding was carried out for six months; among the total clientele of the Child Welfare Centre, the average number who carry out breast-feeding up to the age of six months amounts to 45—50 %. Ignorance and laziness, and in some cases an unwillingness to submit to supervision, are probably the main reasons for failure to join the Child Welfare Centre and for neglect of its instructions. In some cases, however, the fact of being a foreigner or of having recently moved into the district played a part. Practically all the children belonged to the lowest social group (Group III in the Swedish system of classification).

An analysis of the month of birth of the children affected reveals, especially among the cases of tetany, a conspicuous bunching in the three summer months. The reasons for this are under discussion. One factor to which attention should perhaps be paid is the fact that normally no prophylaxis for rickets is given from May to September. During that period the children should be effectively exposed to sunshine; but the children born in the late spring and the summer are often kept so firmly tucked in bed that ultra-violet radiation can hardly reach them. For new-born babies, it might be desirable to give Vitamin D prophylaxis during the summer, as well as in the winter.

E III: 47

Encopresis as a Symptom of Psychic Disturbance

Höök, Kerstin. Pediatric Clinic at Kronprinsessan Lovisas Children's Hospital, Stockholm

Two cases of fecal incontinence are demonstrated. The past history revealed some slight bowel troubles (case I obstipation, case II diarrhœa), but these symptoms have disappeared and now encopresis is the only intestinal symptom. Clinical investigation showed no pathological findings. In both cases other symptoms of neurolability (enuresis, stuttering) were

encountered, and both showed a nonsatisfactory motherchild relationship. During the psychological penetration and treatment of both the child and the mother, the children showed regression into infantile stages (messiness) and gave expression to aggressive tendencies. When a better mother-child-relationship was established the symptoms diminished or disappeared.

In connection with the main theme of the congress, these examples point to the importance of recognizing the pshychic component in encopresis and other intestinal disturbances, and that this component must be considered for successful treatment.

Passage F

F 1: 48

Physical Growth during Infancy

Karlberg, P., and Perman, A. Pediatric Clinic at Norrtull Hospital, Stockholm

In 700 healthy Swedish infants, about 1 300 measurements of length, weight and twelve additional dimensions were recorded. This material was then analyzed to show the body development during infancy.

F 1: 49

Total Hemoglobin and Blood Volume in the Newborn Period

Karlberg, P., Lind, J., Stahlman, M., and Iggbom, S. Pediatric Clinic at Norrtull Hospital, Stockholm

At birth the infant has a hemoglobin concentration of about 19 gm %, but that level falls within the first few months of his life to about 14—12 gm %. The mechanism of this marked fall has been much discussed, and many and varied investigations of the blood volume during the newborn period have been carried out in attempts to elucidate that mechanism.

In most investigations the plasma volume has been determined by some dye method (usually with Evans' blue). Then, from that value and the venous hematocrit, the blood volume was calculated. Blood volume values based on plasma volume determinations have been found by most investigators to be about 100 ml per kilogram, but to vary from 70 in some cases to 150 in others.

The difference in hematocrit values of blood from varied points in the circulatory system influences the calculation of blood volume so as to cause the value based on plasma volume and venous hematocrit to be too high and that based on red cell volume and venous hematocrit to be too low. A more correct value can be obtained if plasma volume and blood cell volume are determined individually and then added. Mollison (1950) found, with such a method, an average value of about 85 ml per kilogram of body

weight in newborn infants during their first day. However, each such determination requires about 10 ml of venous blood (or 3—4 % of the childs total circulating blood volume), and it is doubtful whether one can consider the conditions to be physiological when one follows the blood volume with several repeated examinations.

In order to avoid this difficulty, we have used, at the Norrtull's Hospital in Stockholm, Sjöstrand's CO-method, modified for use with newborn infants, obtaining, thereby, the value for total hemoglobin without the withdrawal of any blood samples what so ever. The principle is this: the child breathes in a closed system containing oxygen and a lesser and exactly known amount of CO. The blood absorbs CO until an equilibrium between the amounts in the blood and in the system is reached, after which the concentration of CO in the system is determined with the help of a CO meter. From that value the amount of absorbed CO and the CO content of the blood can be calculated; on the basis of which the total amount of hemoglobin can be calculated. With this method we have followed the total hemoglobin values in a number of infants from birth until their sixth or seventh weeks, determinations being done about every second day during the first week and later at two week intervals. At the same time, we have done routine hemoglobin determinations. Since total hemoglobin is expressed in grams and routine hemoglobin values are expressed in gram %, the (total hemoglobin: hemoglobin in gm %) × 100 results in the value for blood volume. Surely that will be too low, but since the relation between venous hematocrit and the average hematocrit for the whole body is constant, even with varied hemoglobin concentrations (Mollison —50), that value gives at least the variations in the blood volume. In the cases in which no large amounts of blood are withdrawn for testing, the hemoglobin decreased from 20 to 15—12 gm % at the end of one month. The total hemoglobin, however, remained constant. The blood volume rose after the first two weeks and followed the body weight.

The high hemoglobin concentration of the fetus, giving the blood the ability to carry adequate oxygen despite the low oxygen tension, falls during the newborn period to the level normal for extra-uterine human life. At the same time, the blood volume increases along with the body development. Since the total amount of hemoglobin during this time appears to remain constant, the fall in hemoglobin concentration and the increase in blood volume result in an expected dilution of the blood. During this period the high level of hematopoiesis, present during fetal life, diminishes, only to rise again after the blood dilution has resulted in a lowering of the hemoglobin concentration to the level needed in extrauterine life.

F I: 50

Determination of the Basal Metabolism in Infants, using an Open System

Karlberg, P. Pediatric Clinic at Norrtull Hospital, Stockholm

Description of a method for BM determination in infants, with open system, where the differences in concentration of the oxygen and carbon-dioxide are recorded with a gas analyzer according to Rein (a "Gaswechsels-schreiber"). The method's advantages are discussed. Some experiences of the method are given.

F II:: 51

Some Rare Types of Cardiac and Vascular Malformations

Mannheimer, E., Bengtsson, E., Krämer, R., Warth, J., Wade, G., Wegelius, C., and Winberg, J., Stockholm

1. *Ebsteins disease.* This anomaly consists of a displacement of the tricuspid valve, which is directed downwards into the cavity of the right ventricle. The right auricle is extremely enlarged. The pressure in the lesser circulation is normal. No shunts from left to right are present. The tricuspid valve is mostly insufficient, so that the pressure in the right auricle exceeds that of the left auricle. Some of the patients are slightly blue because of a functioning patent foramen ovale. The prognosis is good. A 3 year old girl with this disease is presented.

2. *Pseudotruncus arteriosus.* This malformation consists of pulmonary atresia and overriding aorta, the pulmonary circulation being provided by a patent ductus arteriosus or by bronchial arteries or by both. There are cases with diminished and with increased pulmonary circulation, depending on the size of the ductus arteriosus and of the bronchial arteries. It is sometimes hard to distinguish this type from a tetralogy of Fallot. Absence of a second pulmonary sound, and a typical angiocardiography are often helpful. A 3 year old girl with this disease is presented.

3. *Pure mitral stenosis of congenital type* (Durossiez' disease). From early infancy symptoms of pulmonary congestion and attacks of pulmonary edema were present. Over the heart a diastolic murmur is heard. On *X-ray* and angiocardiography a large left auricle is seen. *ECG* shows right ventricular hypertrophy and in esophageal leads pathologically increased P-waves. *Catheterization* revealed no shunts and an increased pressure in the lesser circulation.

This case, a girl 1½ year old, is of special interest because of the possibility to perform an operation of the malformed mitral valve. The benefit of such an operation is open to discussion.

4. *Subaortic or valvular stenosis of the aorta in infancy.* A case of a one year old girl is presented. Heart disease was discovered by *X-ray,* which showed a very large left ventricle and auricle. The pulses in both upper and lower extremities were very difficult to feel. The patient was underdeveloped and weighed only 7 800 grams at the age of 1½ year. No murmurs were heard. In this case valvulotomy has been discussed. This

operation has been performed by Bailey in a few cases in adults with valvular aortic stenosis. However the experience is still very limited.

5. *Tumorlike aneurysms of both superior venæ cavæ* (with persistence of a leftsided superior vena cava).

This 4 year old boy showed no signs of cyanosis. He was a little dyspnoeic on exertion. Over the heart a systolic murmur was heard with its maximal intensity over the 3d—4th left interspaces. Before catheterization was performed an X-ray was taken, which showed tumorlike bulges in the upper part of the mediastinum. *Angiocardiography* established the presence of large aneurysmatic dilatations of both superior venæ cavæ. This case is probably not suitable for surgical treatment.

6. *Coarctation of the aorta with multiple cardiac arrhythmias.* This 5½ year old boy represents a typical case of coarctation of the aorta. He was successfully operated upon by professor Crafoord. Both before and after operation the boy got attacks of cardiac arrhythmias. Paroxysmal tachycardia and block of different grade alternated. In the postoperative course ventricular tachycardia and auricular flutter were also seen. The treatment of these different types of disturbances in the cardiac rhythm is discussed.

F II: 52

Congenital Stenosis of the Pulmonary Artery with Septal Defect, but without Overriding Aorta. Its Diagnosis, Differential Diagnosis and Treatment

Krämer, Robert. Pediatric Clinic at Kronprinsessan Lovisas Children's Hospital, Stockholm

Congenital stenosis of the pulmonary artery is usually associated with an interventricular septal defect and with overriding of the aorta. This heart malformation, belonging to the cyanotic group, is well known under the name of Fallot's tetralogy. With the introduction of new investigation technics in this field, particularly heart catheterization and angiocardiography, it became obvious, that pulmonary stenosis without overriding of the aorta is commoner, than was earlier believed. The term pulmonary stenosis without overriding aorta covers Mannheimer's three different types of pulmonary stenosis: pure pulmonary stenosis, pulmonary stenosis with interauricular septal defect and pulmonary stenosis with interventricular septal defect.

From this hospital in cooperation with the St. Eriks Hospital, Stockholm, Mannheimer and associate and Y. Larsson and associate have earlier reported on pulmonary stenosis without overriding aorta, in which there was no significant evidence of a septal defect, describing a total of 30 cases.

In the last three years we have examined 280 cases of congenital heart disease with the heart catheterization method. In this group the diagnosis pulmonary stenosis, without overriding aorta, was made in 51 cases, 35 of them had no evidence of a septal defect, 12 had interauricular and 4 had interventricular septal defects.

The clinical picture of the pulmonary stenosis with septal defect, in cases without cyanosis, usually can not be differentiated from that of the pure pulmonary stenosis. It is characterized by a rough systolic murmur — very often with a thrill — in the pulmonary area, sometimes diminished second sound, in the X-rays the pulmonary arc is bulging more or less, the right ventricle is marked and in the lungfields there are less vascular markings than normal. The Ekg shows more or less marked right axis deviation and signs of right ventricular hypertrophy.

The differentiation of pulmonary stenosis with septal defect from the pure type is possible only by heart catheterization. If there is a left to right shunt through the septal defect, it can be established by finding a significantly higher oxygen content in the auricular or ventricular blood than in the superior vena cava blood. If there is a right to left shunt the oxygen saturation of the systemic arterial blood is decreased, lower than 95 %, and below a certain degree cyanosis is present. If there is a right to left shunt, the presence of cyanosis will depend on the pressure gradients of both the right and the left chamber of the heart, which are connected by a septal defect. It may happen in the course of life that changing of the pressure gradients may convert a left to right shunt into a right to left shunt with the development of cyanosis. Exertion can also produce, in this way, cyanotic attacks. Five out of the 12 cases of pulmonary stenosis with interauricular septal defects had cyanosis at rest, 2 others only after exertion, and in the other 5, cyanosis was never observed. The 4 cases of pulmonary stenosis with interventricular septal defect were acyanotic. The degree of the pulmonary stenosis, which is mostly valvular, and the size of the septal defect plays an important rôle, in determining the presence or absence of cyanosis.

The cyanotic form of pulmonary stenosis with a septal defect may sometimes be easily mistaken for Fallot's tetralogy, especially a tetralogy of Fallot combined with an interauricular septal defect.

The differentiation may also be nearly impossible to make by angiocardiography, the contrast media passing to the left side of the heart, simulating the overriding of an aorta filled early with contrast. Only very careful investigation, using all available methods can make the differential diagnosis clear.

It is of very great importance to make the differentiation, because the Blalock-Taussig operation, which by anastomosis increases the blood flow to the lungs and which is so useful for the relief of the Fallot patients, cannot be used in pulmonary stenosis without an overriding aorta. The burden on the left heart is too great, and most of the few patients in whom the operation has been tried, died in left heart failure.

On the whole, the prognosis in cyanotic pulmonary stenosis is as bad as in the tetralogy of Fallot, if there is no surgical treatment. Fortunately in the last years a valvulotomy was developed by Brock, by which the stenosed pulmonary valves can be incised or dilated.

F III: 53

Child Welfare Work in Sweden

Ström, Justus. Kungl. Medicinalstyrelsen, Stockholm

Child Welfare Work in Sweden started in 1901 on private initiative. In 1938 Government and county councils assumed this activity, and today the organization embraces the whole country. At the same time care for sick children has swiftly developed. At the exhibition we have a map of Sweden where the children's hospitals and the most important welfare centres are marked. You will, further, find statistics regarding the extension of health care for pre-school age children.

Contrary to many other countries we try to make use of specialists as far as possible, also in preventive work.

The change of the mortality-rate among infants and small children in Sweden in the twentieth century appears from the curves. The remarkable decrease can be ascribed to an amelioration of living standards in general, to improvements of hygiene and medical attendance, education of the public, and to social and economical development. By means of a large-scale information campaign the organized health care for children has done much towards the reduction of infant mortality.

In 1900, infant mortality amounted to 15.8 % of the total mortality — in 1949 it was 4.1 %. A third of the reduction in the mortality rate in general can be put down to the decreased rate of mortality among infants. In 1950 the infant mortality rate was 22.3 ‰.

The graphic curves make it clear that in infant mortality it is the neonatal mortality rate which dominates nowadays, owing above all to the mortality among premature children.

Other curves show from which diseases the infants and the small children die. The decrease of the mortality rate is especially striking when we come to the various infectious diseases, diseases of the respiratory organs and to gastroenteric disturbances.

Room D

D: 54

Extended Application of Angiocardiography as an Examination Method

Lind, J., and Wegelius, C. Pediatric Clinic at Norrtull Hospital, Stockholm

With an angiocardiographic technique, characterized by an exposure rate of 10 pictures per second, synchronously in each of two planes, with a simultaneous registration on an Ekg-tracing of the precise moment of each exposure, it is possible to visualize and to study cardiac dynamics. In addition to the advantages afforded by this method with its clearer visualization of anatomic changes of significance in roentgen diagnosis, it has also

provided unique data, pertinent to the clarification of the physiology and the pathological physiology of the heart. These data are illustrated by several varied and typical cases.

D: 55

Ileus in the Newborn

Ehrenpreis, Th. Surgical Department, Kronprinsessan Lovisas Children's Hospital, Stockholm

The problems to be dealt with in intestinal obstruction of the newborn are two-fold; prompt recognition of the condition and adequate treatment. Both are of equal importance for the result of the treatment. The diagnosis is essentially roentgenological. The purpose of this exhibition is to demonstrate the routine method of roentgenologic examinations as adopted at the Kronprinsessan Lovisas Children's Hospital, and the results of the examinations, the typical X-ray pictures of the different forms of intestinal obstruction in the newborn.

D: 56

Osteomyelitis in Children. A Follow-up Study

Andersson, Å., and Sandegård, E. Surgical Department, Kronprinsessan Lovisas Children's Hospital, Stockholm

A series of X-ray-films, demonstrates the course of osteomyelitis in infancy and childhood. The children have been treated in Kronprinsessan Lovisas Children's Hospital during the period 1940—1950.

All the cases have been treated either with sulfa, antibiotics, heparin or with different combinations of these preparations. About half of the cases were treated surgically. In the acute phase the treatment consisted in incision of subcutaneous abscesses. Most of these patients were completely cured. In a few cases the disease passed into a chronic stage with bone abscesses or sequestration. These cases have had additional surgical therapy (opening of the bone abscess, sequestrotomy and bone transplantation) with subsequent healing.

INDEX

Sid.

Presidium of the Congress 3
Executive Council af the Congress 3
Members of the Congress 4
Minutes of the Proceedings 12
Presidential Address 17
Lectures and Discussions 25
General Meeting 126
Scientific and Industrial Exhibition 129

LECTURES AND EXHIBITIONS

A

Acrodynia, Caused by Exposure to Mercury 123
ACTH, Influence on the Eosinophil Count in Gastroenteritis 115
Total and Extracellular Body Water during Treatment 79
Treatment of Acute Rheumatic Fever 110
Ahnsjö, S. 25
Ahvenainen, E. K. 71, 171
Allergy, Function of the Suprarenal Cortex in Allergic Diseases 116
Leukocytolysis in Vitro 120
Amlie, R. 67
Ammonium Chloride Acidosis, on the Action of Insulin in Dogs 159
Andersen, B. 123
Andersen, H. 147
Andersen, O. 37, 78
Andersson, Å. 200
Anemia, Megaloblastic in Children 82, 178
Angiocardiography, Extended Application of 199
Antibody Situation, in Premature Children 182
Arajärvi, T. 68, 69
Arvidson, M. 182
Asphyxial Membranes in Lungs of Newborns 71
Asthma, as s Psychosomatic Symtom 45
Psychosomatic Investigations 52
Auken, K. 64, 165
d'Avignon, M. 122, 158, 175

B

Basal Metabolism, Determinations of, Using an Open System 194
BCG Vaccination of Elementary School Children 184
Bengtsson, E. 194
Berezin, D. 187
Berfvenstam, R. 172
Bjelkhagen, I. 153
Bierring-Sørensen, K. 51
Bjuggren, G. 183
Blood Minerals, in Pyloric Stenosis 74
Blood Volume, See Total Hemoglobin 190
Body Water, Total and Extracellular during ACTH Treatment 79
Boesen, I. 51, 89
Bottles for Collecting Urin from Infants 148
Brachyoesophagus and Insufficiency of Cardia in Children 73

Sid.

Braestrup, P. W. 57, 75, 79
Brandt, H. 65
Brandt, S. 65, 68
Broman, B. 187
Bülow, K. 52

C

Carbonic Anhydrase, See Premature Children 172
Cardiac and Vascular Malformations:
Some Rare Types of 194
Congenital Malformation of the Heart, Type Distribution 89
Congenital Stenosis of The Pulmonary Artery with Septal Defect, but without Overriding Aorta 195
Cerebral Complications Following Acute Respiratory Diseases 153
Child Welfare Work in Sweden 199
Chloromycetin and Skin Test in Pertussis 182
Chylomicronaemia, Alimentary 76

D

Diabetes:
Late Vascular Complications 145
Late Complications, Liver Function and Diet 146
Skeletal Age in Diabetic Children 125
Drucker, P. 51
Dupont, A.-L. 95

E

Eating Problems in Children 61
Ehrenpreis, Th. 200
Electroencephalography,
Findings in Patients with Cerebral Palsy 65
Hypocalcemia due to Hypoparathyroidism 164
In Children with Acute Head Injury 177
In Children with Epileptic Fits 176
Influence of Emotions upon 175
In Congenital Hypothyroidism 175
In Infectious Diseases 176
Electron Microscopic Studies of Tubercle Bacilli 181
Electrophoretic Studies of Blood Serum from Rabbits 147
Encopresis as a Symptom of Psychic Disturbance 189
Enell, H. 108, 184
Engleson, G. 146
Enuresis by Schoolchildren 62
Eosinophil Count, Influence of Epinephrine and ACTH in Gastroenteritis 115
Ericsson, H. 160
Eriksson-Lihr, Z. 54, 116
Ermala, P. 76
Escherichia Coli, Occurrence in Diarrhaeal Disease and in a Control Material 95

F

Fagerberg, S. 159
Farup, B. 52, 53
Fat Emulsions, use of Intravenous 76
Fog, E. 51
Foght-Nielsen, K.-E. 56
Forsander, O.-A. 171
Frandsen, F. 61

Sid.
Frey, T. 176
Friderichsen, C. 99
Friis-Hansen, B. 79
Fürstenberg, N. 163

G

Gargoylism, a Case of 151
Gedda, E. 55
Gladnikoff, H. 124
Growth, Judgement after a "grid-method" 91
Physical during Infancy 190
Grönroos, J. 96
Guest, G. N. 159
Gunnarson, S. 48, 62
Gyllenswärd, Å. 177
Görtz, G. 51

H

Hagberg, B. 163, 181
Hagelsteen, H. 122
Hahn, B. 102
Hallman, N. 96
Halonen, V. 76
Hamne, B. 55
Hand-Schüller-Christan, a Case of 181
Hansted, Chr. 164
Hedlund, P. 182
Hedman, S. 108, 181
Heikel, P.-E. 125
Heinild, S. 47, 51
Hellström, B. 119
Helminen, S.-L. 62
Henriques, A. 51
Herlitz, G. 106
Hernberg, C. A. 125
Hesselvik, L. 109, 160
Hestetun, S. 100
Holmdahl, K. 170
Holmdahl, S. 153
Holmgren, B. 176
Hyalyronidas, Facilitating Intramuscular Urography 124
Höök, K. 189

I

Iggbom, S. 190
Ileus in The Newborn 200
Imerslund, O. 82, 178
Immunity, Duration of, Following Vaccination against Diphteria 160
Infant Mortality, An Attempt to Combat 169
Intravenous Iron Treatment 181
Ironbinding Capacity of Serum, Influence of Infectious Diseases 163
Iversen, T. 59, 65

J

Jacobsson, E. 124
Jacoby, P. 61
Jelke, H. 151

Sid.

Jonsson, B. 110
Juel-Nielsen, N. 59
Jäykkä, S. 56

K

Kaiser, K. 148
Karlberg, P. 94, 190, 194
Karlén, K.-H. 111, 181
Kauhtio, J. 74, 75
Klackenberg, G. 175
Kraepelin, S. 183
Kreutzfeld, H. 51
Krämer, R. 194, 195
Kåss, A. 81 106

L

Larsson, L.-E. 175, 177
Larsson, Y. 145, 152
Leukocytolysis, in Vitro in Allergy 120
Lichtenstein, A. 145
Lichtenstein, H. 159
Lind, J. 72, 90, 183, 190, 199
Lindblad, Y. 153
Linder, U. 175
Lindquist, B. 87
Lingen, Chr. 108, 147, 181
Louhivuori, A. 171

M

Mackler, B. 159
Madsen, A. 51
Malm, E. 70, 72, 171
Mannheimer, E. 90
Megaloblastic Anaemia, Red Blood Cell Diameters 82
Melin, K. A. 66, 104, 108, 175, 177, 181
Menarche
  Attending Mental Reactions 64
  Factors influencing the age 63
Meningitis, Late Sequelae of Hemophilus Influenzae Meningitis 100
  Result of the Treatment of Tuberculous Meningitis 103
Morbus haemolyticus neonatorum, in One of Dizygotic Twins 81
  Rh-testing 187
Mossberg, H.-O. 62, 182
Munkvad, I. 56

N

Niemineva, K. 171
Nilsby, I. 153
Nyren-Brenel, B. 188

O

Obesity, Psychosomatic 59
Olsson, W. 94
Ortmann, G. 51

Sid.

Osteomyelitis in Children 200
Osteopetrosis 83
Oxygen Treatment in Childhood 152
In Neonatal Asphyxie 163

P

P^{32}, Renal Excretion of 154
Pettay, O. 120
Pettersson, G. 73
Perman, A. 190
Ploman, K. G. 145
Plum, P. 50
Pneumonia, Calcium Metabolism in Plasma Cell Pneumonia 96
Therapy 98
Precocious Puberty Granulosà-cell Tumor 121
Premature Infants
Antibody Situation in 182
Capillarymicroscopic Examinations of the Conjunctiva Capillaries .. 68
Carbonic Anhydrase in the Blood 172
Fat Absorption: Influence of Heat Treatment of Milk 172
Physiological Aspects of the Oxygen Treatment 70
Prematures 171
Some Principles of Treatment 170
T_m for PAH and Glucose 78
Psychosomatic disease in Pediatric:
Asthma as a Psychosomatic Symtom 45
Methods of Work in Psychosomatic Pediatrics 44
Overcrowded Flats as Aethiological Moment of Behaviour Diseases .. 51
Present Tasks of Psychosomatic Pediatrics 47
Psychosomatic Disease in Childhood 37
Psychosomatic Disorders in Pediatric 25
Psychosomatic Investigations of Asthmatic Children 52
Psychosomatic Obesity 59
Some Experience from Psychiatric Work in a Pediatric Unit 48
Testmeal Research and Its Psychosomatic Background 56
Treatment with Special Reference to Treatment Primarily of the Mothers 57
Upper Respiratory Tract Infections from a Psychosomatic Point of View 56
Pyruvic Acid, Content in the Blood of Healthy Children 77
Pyloric Stenosis, Blood Minerals in 74

Q

Quaade, F. 59

R

Radioactive Iodine in the Diagnosis of Hypothyroidism 158
Radioiodine Absorption and Excretion in Healthy and Diseased Children 122
Ranström, S. 71
Rantasalo, I. 171
Rasmussen, J. 51
Reiler, R. 98
Reinand, T. 176
Retrolental Fibroplasia in Sweden 153
Rheumatic Fever, Treatment with ACTH and Cortisone 110
Rickets, Cases of Rickets and Tetany, Gothenburg, 1946—1950 188
Effect of Vitamin D on the Metabolism of Radiocalcium 87
Metabolic Disturbances in the Skeleton 86

Sid.
Rickets, Occurence during Fetal Life 187
Ricklefs, G. 57
Rinvik, R. 114, 121
Rosén von Rosenstein, To the Memory of 145
Räihä, C.-E. 50, 78, 87, 118, 166, 171

S

Salmi, T. 114
Salomonsen, L. 67, 72, 119
Sandegård, E. 200
Schondel, A. 51
Selander, P. 72, 75
Seleste, E. 69
Serum Amylase in Children 147
Serum Content of Fe after Injections of Diphteria Antitoxin 166
Silfverskiöld, B. 177
Simell, G. 63
Sinusitis in Apparently well Children 183
Skaug, O. 122
Skeletal Age in Diabetic Children 125
Smith, T. 51
Stahlman, M. 190
Ström, J. 199
Ström, L. 154, 158
Sundal, A. 83
Suprarenal Cortex, Function in Allergic Diseases 116
Suprarenal Glands, Roentgenologic Examination of 159
von Sydow, G. 187
Söderhjelm, L. 172

T

Tallqvist, H. 77, 78, 171
Temperature, Rhythm of, Studied with Continous Registration 177
Tetany, See Rickets 188
Tolstrup, K. 59
Total Hemoglobin and Blood Volume in the Newborn Period 190
Toxoplasmosis, the Frequency of congenital 153
Triple Vaccination in Infancy 109
Tubercle Bacilli Calmette Vaccine, Labelled with Radioactive Phosphorus 154
Dissemination of, after Intracutanous Injection of Calmette Vaccine 158
Influence of various remedies upon 108
Tudvad, F. 78, 79
Tunevall, G. 183
Turunen, S. 166
Tähkä, H. 115, 119

U

Ugland, J. 118

V W

Waal, N. 52, 53
Vaccination, Triple, in Infancy 109
Wade, G. 194
Vahlquist, B. 51, 78, 83, 109, 163, 182
Warth, J. 194
Wasz-Höckert, O. 103, 108

Sid.

Wegelius, C. 72, 90, 194, 199
Vendel, S. 89, 91
Wergeland, H. 45
Vesterdal, J. 78, 79, 114, 120
When and Where do Girls Acquire their Knowledge of Sex 165
Widström, G. 154
Wilken-Jensen, K. 52
Winberg, J. 194
Vuoristo, G. 44

Y

Ylppö, A. 70, 71

Z

Zetterström, R. 86

Å

Åkerrén, Y. 72, 75, 99, 121, 163, 169

Ö

Ödegård, A. 91
Öhrberg, G. 175, 177
Öhrberg, Kj. 175, 177
Østergaard, L. 59

ZEISS

Standard-Mikroskop

är en nykonstruktion där nya erfarenheter i stativets utformning förverkligats. Djupliggande koaxiallagrade grov- och fininställningar möjliggör mycket bekvämt arbetssätt. Den i stativfoten inbyggda belysningen möjliggör i samband med den nykonstruerade kondensorn full utlysning av synfältet vid varje förstoring. Korsbordet med koaxialt anordnade drev möjliggör bordets rörelse i båda riktningarna samtidigt. Absolut säkert preparatskydd genom fjädrande objektiv. Utbyggbart med faskontrast.

ZEISS SVENSKA AB, KUNGSGATAN 33, STOCKHOLM
TEL. 23 09 65

Rondase

SPRIDNINGSFAKTORN

Värdet av hyaluronidas för hypodermoklys och i många andra fall, där ökad spridning och snabb absorption av subkutant injicerade vätskor är önskvärd, är numera allmänt erkänt. Evans tillhandahåller detta enzym i frystorkad form, karakteriserat av:

1. Hög renhetsgrad — främmande äggviteämnen och salter ha i största utsträckning avlägsnats. Tillsats av lösningsmedel till innehållet i en ampullflaska ger omedelbart en absolut klar lösning.

2. Hög aktivitet — löses innehållet i en ampullflaska i 1 ml sterilt vatten, är denna lösning aktiv ännu i spädning 1: 50 000.

3. Konstant verkningsstyrka hos innehållet i varje ampullflaska.

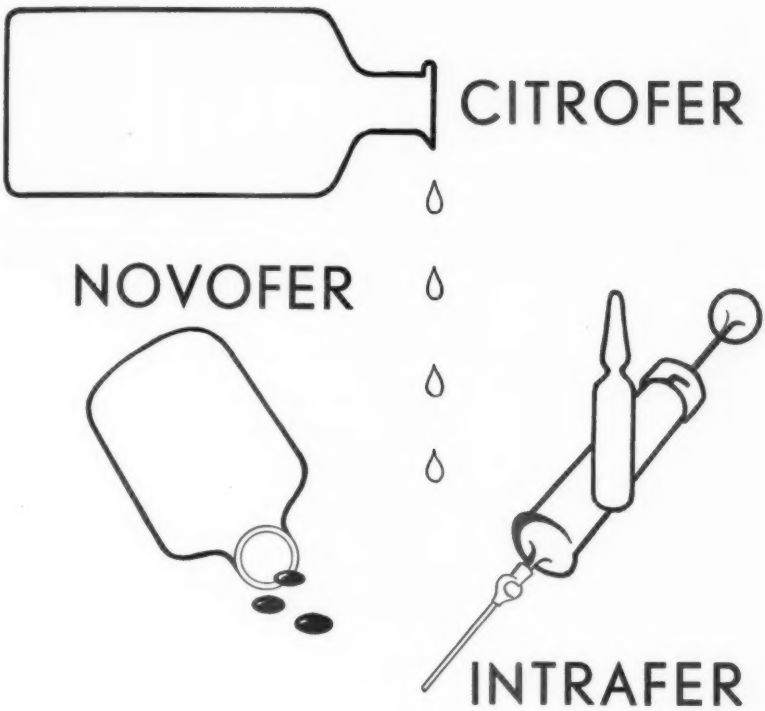
Vidare upplysningar på begäran genom

ENEQVIST, HOLME & CO. AB, STOCKHOLM

Tillverkat i England av

EVANS MEDICAL SUPPLIES LTD

LIVERPOOL OCH LONDON



högvärdiga järnpreparat
för effektiv terapi

PHARMACIA UPPSALA

— vetenskap och industri hand i hand

Aminosol
Vitrum

Amino acid preparation
for peroral and parenteral nutrition

Indications for **peroral** therapy with Aminosol

Premature infants, gastroenteritis, ulcerative colitis, hypoproteinemia, food allergy, fibrosis of the pancreas, nephrosis and convalescence

Indications for **parenteral** therapy with Aminosol

Postoperatively, obstruction of the alimentary canal, peritonitis, oesophagitis, severe gastritis and gastroenteritis, ulcerative colitis, anorexia severe cases of undernourishment, burns oedema of the gastrointestinal tract, severe diarrhoeas and acute infections, particularly in children

Vitrum *Stockholm*

MC

— i folkhälsans tjänst

MJÖLKCENTRALEN STOCKHOLM

Ge Baby CLAPP'S

världens mest sålda babymat

Clapp's Barnmat har framgångsrikt använts under två generationer. Svensk teknik och svenska barnläkare i samarbete med amerikansk vetenskap och amerikansk praktisk erfarenhet har av svenska råvaror här fått fram en barnmat som är

o ö v e r t r ä f f a d.

Tillverkas av

Sirius
GÖTEBORG

i samarbete med American Home Foods, Inc. USA

TEAMWORK IN MEDICINE, CHEMISTRY AND PHARMACY

The basis for our success is our close and personal relationship with physicians and other scientists. The research work carried out in our modern laboratories is directed by the leading specialists of the day. Their scientific knowledge combined with our technical resources form a perfect team which ensures that our products are in complete accord with the most recent medical advances.

AKTIEBOLAGET LEO HÄLSINGBORG
SWEDEN

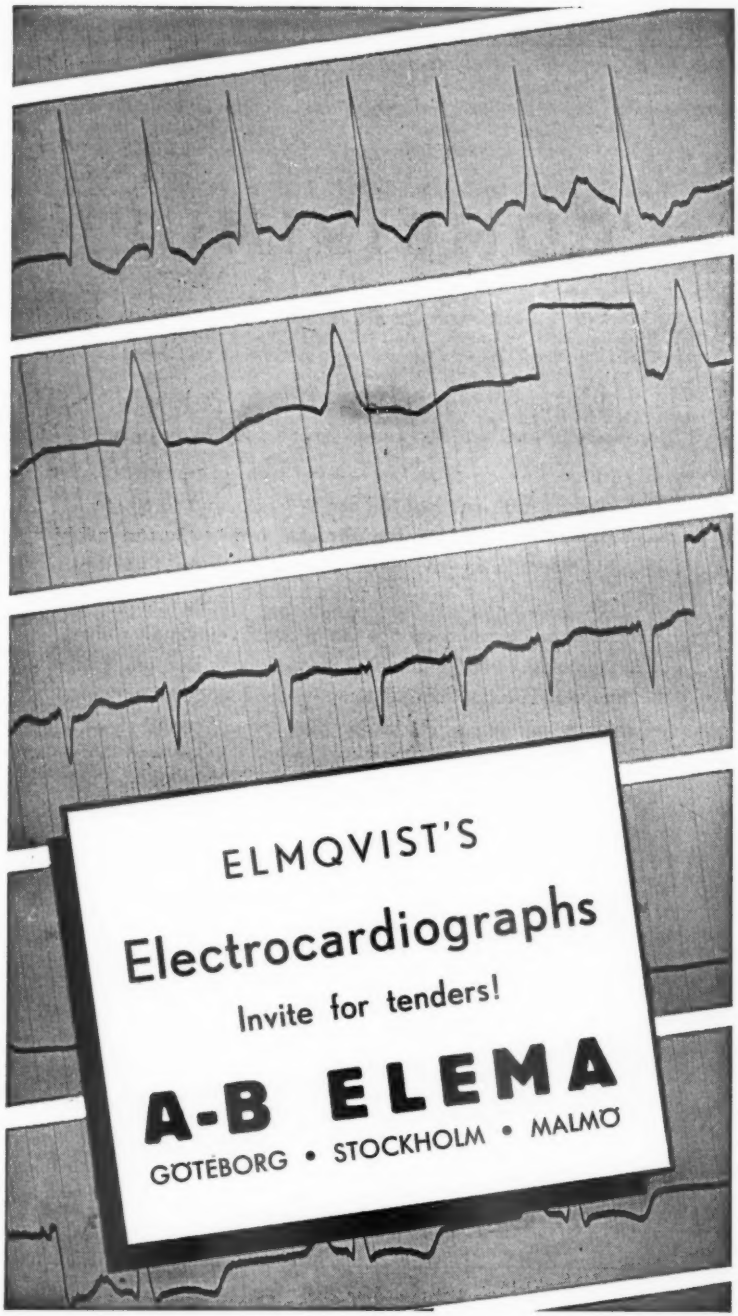
NESTLÉ

at the service of childhood . . .

. . . the principle that guided Henri Nestlé in the past, and which has been characteristic of Nestlé's for over three quarters of a century.

Today the name of Nestlé's is renowned for quality throughout the world. This high standard is maintained by the constant improvement of Nestlé manufacturing methods and processes, coupled with the ever-increasing experience of its research and control laboratories.

However, it must be stressed that the vast range of Nestlé's specialities for the feeding and the dietetic treatment of children could not have been created had Nestlé not been guided by another principle, namely close contact with the Medical Profession. With these products, which are all well known to pediatricians, Nestlé maintains its position at the head of infants' dietetics.


ELMQVIST'S
Electrocardiographs
Invite for tenders!
A-B ELEMA
GÖTEBORG • STOCKHOLM • MALMÖ

'COMBIVIMIN'

LØSNING

'Combivimin' håller vitaminerna A, B_1, B_2, nikotylamid (PP-faktorn), C och D_2 i en klar, stabil, alkoholfri lösning

De i 'Combivimin' ingående A- och D-vitaminerna föreligger i vattenlöslig form, vilket är en värdefull nyhet, eftersom härigenom resorptionen av dessa vitaminer starkt förbättras

Preparatet är välsmakande och lätt att intaga direkt eller efter spädning med vatten, mjölk eller annan dryck. Det kan även blandas med 'Beviton' och 'C-vimin' syrup. Mängden av varje vitamin pr ml lösning motsvarar det normala dagsbehovet.

'Combivimin' lösning är särkilt värdefull i barnpraxis.

'Combivimin' lösning tillhandahålles i följande förp. och pris:
flaska à 30 ml med graderad pipett .. kr 4:80

ASTRA

34. **Sällström, Thor,** Die akute Nierenentzündung und ihre Prognose bei Scharlacherkrankungen. **Leeuw, K. De,** The Prognosis of Nephritis in Children. Sw. Cr. 5: —.
35. **Lindquist, Nils,** Studien über die cutane Capillarresistenz im Kindesalter. Sw. Cr. 5: —.
36. **Lange, Cornelia de,** Studien über angeborene Lähmungen bzw. angeborene Hypotonie. Sw. Cr. 3: —.
37. **Forssell, P.,** Klinische und histologische Untersuchungen über die sog. Hexenmilchsekretion. Sw. Cr. 3: —.
38. **Söderling, Bertil,** Zur Früh- und Spätprognose der Säuglings- und Kleinkindertuberkulose, zugleich eine Studie über die Epituberkulose (Eliasberg-Neuland). Sw. Cr. 5: —.
39. **Soveri, Vuokku,** Der Verlauf der Luft durch den Verdauungskanal des Säuglings. Sw. Cr. 3: —.
40. **Selander, Per,** Epidemischer und sporadischer Ikterus. Sw. Cr. 5: —.
41. **Salomonsen, Leif,** Morbus hemorrhagicus neonatorum. Sw. Cr. 3: —.
42. **Leppo, Varpu,** Über den Einfluss der Rübe (Brassica Rapa) auf die Azidität des Harns und des Stuhls bei gesunden und magendarmkranken Säuglingen und Kindern. Ein Beitrag zur Rohkost bei Kindern. Sw. Cr. 3: —.
43. **Brander, T.,** Contents 8 Different Articles. Sw. Cr. 3: —.
44. **Mannheimer, Edgar,** Calibrated Phonocardiography and Electrocardiography. A clinical-statistical study of normal children and children with congental heart disease. Sw. Cr. 5: —.
45. **Ahnsjö, Sven,** Delinquency in Girls and its Prognosis. Sw. Cr. 5: —.
46. **Hamne, Bertil,** Studien über die Biologie des C-Vitamins mit besonderer Berücksichtigung des Kohlehydratstoffwechsels. Sw. Cr. 5: —.
47. **Vahlquist, Bo C:son,** Das Serumeisen. Eine pädiatrisch-klinische und experimentelle Studie. Sw. Cr. 10: —.
48. **Wilton, Ake,** Gewebsbiologische Studien über die Pathogenese der Addison-Biermer'schen Anämie. Sw. Cr. 5: —.
49. **Herlitz, Gillis,** Studien über die sog. initialen Fieberkrämpfe bei Kindern. Sw. Cr. 5: —.
50. **Wåhlin, Olof S.,** Über die Methodik bei der Ausführung der Tuberkulinreaktionen sowie über die Verbreitung der Tuberkulinallergie bei Schulkindern im nördlichen Schweden (Västerbotten). Eine statistische Analyse. Sw. Cr. 5: —.
51. **Brandberg, Olof,** Studien über das klinische Bild der Leukosen und der sog. leukämoiden Reaktionen im Kindesalter. Sw. Cr. 5: —.
52. **Edgren, Gunnar,** Prognose und Erblichkeitsmomente bei Eczema infantum. Sw. Cr. 5: —
53. **Roos, Bertil,** Über die Karies des Milchgebisses bei Kleinkinder. Mit besonderer Berücksichtigung der Bedeutung einiger sozialer und medizinischer Faktoren. Eine sozialmedizinische Studie aus Südschweden. Sw. Cr. 5: —.
54. **Broman, Birger,** The Blood Factor Rh in Man. A Clinico-serological Investigation with Special Regard to Morbus Haemolyticus Neonatorum (»Erythroblastosis foetalis»). Sw. Cr. 5: —.
55. **Peitsara, Heikki,** Tierexperimentelle Rachitisuntersuchungen mit besonderer Berücksichtigung der Muskeltätigkeit. Sw. Cr. 5: —.
56. **Rinvik, Roald,** BCG-Vaccination in Children, The effectivity and some immune biological manifestations. Sw. Cr. 5: —.
57. **Elgenmark, Olle,** The Normal Development of the Ossific Centres during Infancy and Childhood. A clinical, roentgenologic, and statistical study. (Out of print.)
58. **Sydow, Gert v.,** A Study of the Development of Rickets in Premature Infants. (Out of print.)
59. **Kaijser, Kurt,** Gastric Juice Examinations in Children. A clinical-physiological study. Sw. Cr. 3: —.
60. **Gunnarson, Siv,** Some Types of Nervous Disorders in Children and their Prognosis. An investigation based on the study of hospital material, followed up by subsequent examination. Sw. Cr. 3: —.
61. **Otterström, Edith,** Delinquency and Children from Bad Homes. A study of their prognosis from a social point of view. Sw. Cr. 5: —.
62. **Carlgren, Lars-Erik,** Gallop Rhythm in Children. Studied by means of calibrated phonocardiography. An experimental and clinical investigation. Sw. Cr. 3: —

63. **Jacobsson, Erik,** Rheumatic Fever with Chorea Minor. A clinical study with special reference to the prognosis. Sw. Cr. 5: —.
64. **Landtman, Bernhard,** Heart Arrhythmias in Children. Sw. Cr. 3: 50.
65. The Proceedings of the Eighth Northern Pediatric Congress. Helsingfors June 27—June 29, 1946. Sw. Cr. 5: —.
66. **Mossberg, Hans-Olof,** Obesity in Children. A clinical-prognostical investigation. Sw. Cr. 5: —.
67. **Ahvenainen, E. K.,** On Changes in Dilatation and Signs of Aspiration in Fetal and Neonatal Lungs. Sw. Cr. 5: —.
68. **Wegelius, Ruth,** On the Changes in the Peripheral Blood Picture of the Newborn Infant immediately after Birth. Sw. Cr. 5: —.
69. **Vendel, Stephan,** Cow's Milk Idiosynerasy in Infants. Sw. Cr. 3: —.
70. **Werner, Birgitta,** Peptic and Tryptic Capacity of the Digestive Glands in Newborns. A comparison between premature and full-term infants. Sw. Cr. 3: —.
71. **Maasik, Elisabeth,** Über die Einwirkung der Kälte auf das periphere Blutbild des Säuglings. Experimentelle Untersuchungen. Sw. Cr. 5: —.
72. **Otila, Eino,** Studies on the Cerebrospinal Fluid in Premature Infants. Sw. Cr. 5: —.
73. **Hirvensalo, Mikko,** On Hemorrhages of the Medulla Oblongata and the Pons and on Respiratory Disorders in Premature Infants. Sw. Cr. 5: —.
74. **Hesselvik, Lennart,** Respiratory Infections among Children in Day Nurseries. Sw. Cr. 5: —.
75. Papers from Kronprinsessan Lovisa's Children's Hospital. Sw. Cr. 5: —.
76. **Lewis-Jonsson, Johannes,** Chorea. Its Nomenclature, Etiology, and Epidemiology in a Clinical Material from Malmöhus County 1910—1944. Sw. Cr. 5: —.
77. The Proceedings of the Ninth Northern Pediatric Congress, Copenhagen August 13—August 16, 1948. Edited by **Paul Drucker.** Sw. Cr. 5: —.
78. **Somersalo, Olli,** Staub Effect in Children. Studies of the blood sugar regulation by means of double and triple glucose tolerance tests. Sw. Cr. 5: —.
79. **Wasz-Höckert, Ole,** The Tuberculin Reaction in Different Parts of the Skin and the Sensitivity in Rheumatoid Arthritis. With special reference to the technical error in the Mateux reaction. Sw. Cr. 5: —.
80. **Frisell, Erik,** Studies on Bacterium Bifidum in Healthy Infants. A clinical Bacteriological Investigation. Sw. Cr. 5: —.
81. **Tähkä, Hilkka,** On the Weight and Structure of the Adrenal Glands and the Factors Affecting Them, in Children of 0—2 Years. Sw. Cr. 5: —.
82. **Ström, Lars,** Studies of the Renal Excretion of P^{32} in Infancy and Childhood. Sw. Cr. 5: —.

Pris kr. 10: —